

Cost-Effectiveness of Vaccination and the Value of Prevention

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To my parents, Ulrika and Göran, with all my love.

*Economy is half the battle of life;
it is not so hard to earn money as to spend it well.*

- C.H. Spurgeon -

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ABSTRACT

The overall aim of this thesis was to analyse the cost-effectiveness of vaccination of infectious diseases and to investigate the value of prevention, in a Swedish setting.

This thesis consists of five studies. In Study I through IV, decision analytical modelling was applied to economic evaluations of the cost-effectiveness of vaccination or vaccination strategies against infectious diseases. Study I investigated the cost-effectiveness of sex-neutral HPV vaccination compared to girls-only vaccination, and Study II examined the cost-effectiveness of different vaccination strategies for pertussis. Study III investigated the cost-effectiveness of pneumococcal vaccination of the elderly, and Study IV the cost-effectiveness of varicella and/or herpes zoster vaccination among children and the elderly. There are no official cost-effectiveness thresholds in Sweden or guidelines on the relative cost-effectiveness of prevention in relation to treatment. Study V used contingent valuation and a two-part model to investigate whether, and how, the willingness to pay for prevention differed from the willingness to pay for treatment.

Overall, the results from the four economic evaluations suggest that vaccinations lead to a reduced burden of disease and that the cost-effectiveness often was heavily influenced by the values of the included parameters, as the price of the vaccine, the applied time horizon, and model choice. Finally, the results from Study V suggest that prevention was, on an average, valued higher than treatment.

Keywords: health economics, economic evaluation, cost-effectiveness, vaccination, prevention, contingent valuation

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SAMMANFATTNING PÅ SVENSKA

Hälsoekonomi är en disciplin inom nationalekonomi som, bland annat, analyserar och bedömer kostnader och hälsoeffekter av insatser inom hälso- och sjukvården. Eftersom samhällets resurser är begränsade, samtidigt som efterfrågan på hälsa är oändlig, är prioriteringar nödvändiga inom hälso- och sjukvården. Hälsoekonomiska utvärderingar som utförs på ett metodiskt sätt underlättar dessa prioriteringar och gör dem mer transparanta.

En av de vanligaste analyserna inom hälsoekonomiska utvärderingar är kostnadseffektivitetsanalyser, vilka jämför kostnader och hälsoeffekter av en intervention jämfört med ett jämförelsealternativ. Resultaten från en kostnadseffektivitetsanalys presenteras ofta i form av kostnad per vunnet kvalitetsjusterat levnadsår (QALY). QALY är ett mått som väger samman hälsorelaterad livskvalitet och livslängd.

Den här avhandlingen syftar till att analysera kostnadseffektiviteten av vaccinationer och vaccinationsstrategier mot infektionssjukdomar inom ramen för det svenska vaccinationsprogrammet. Avhandlingen syftar också till att undersöka hur betalningsviljan ser ut för preventiva insatser, såsom vaccination, i jämförelse med behandling, för hälsoförbättringar av samma storlek.

Delstudie I innehåller en kostnadseffektivitetsanalys av könsneutral HPV-vaccination och finner att det är kostnadseffektivt att vaccinera pojkar i tillägg till flickor inom ramen för det nationella vaccinationsprogrammet. I delstudie II undersöks kostnadseffektiviteten av olika vaccinationsstrategier (kokongvaccination, vaccination av gravida och vaccination av barn vid exakt rätt tidpunkt i programmet) för att skydda spädbarn från kikhosta. Resultaten visar att den mest kostnadseffektiva strategin är att vaccinera barn vid exakt rätt tidpunkt i programmet. Delstudie III undersöker kostnadseffektiviteten av pneumokockvaccination av 65-åringar och 75-åringar. Resultaten från den studien indikerar att det inte är kostnadseffektivt att vaccinera 65-åringar mot pneumokocker, men att det kan vara det för 75-åringar. Den fjärde delstudien (delstudie IV) undersöker kostnadseffektiviteten av vattkoppvaccination och bältrosvaccination eller ett kombinerat program med både vattkopps- och bältrosvaccination. Resultaten visar att det skulle vara kostnadseffektivt, och även kostnadsbesparande, att vaccinera barn mot vattkoppor, men inte 65-åringar mot bältros.

Resultaten från delstudie V, i vilken en enkät användes för att undersöka den relativa betalningsviljan för prevention i jämförelse med behandling, visade att respondenterna i studien i genomsnitt hade en 85 % högre betalningsvilja för prevention jämfört med behandling. Det medför att samhällets betalningsvilja för vaccination i varje fall inte borde vara lägre än vad som appliceras inom andra områden av hälso-och sjukvården.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Wolff E, Elfström KM, Haugen Cange H, Larsson S, Englund H, Sparén P, Roth A. *Cost-effectiveness of sex-neutral HPV-vaccination in Sweden, accounting for herd immunity and sexual behaviour*. Vaccine 2018;36:5160-5165
- II. Wolff E, Aronsson B, Hultstrand M, Brouwers L. *Cost-effectiveness analyses of different vaccination strategies to reduce pertussis among infants in Sweden*. Journal of Infectious Diseases and Epidemiology 2019;5:065
- III. Wolff E, Storsaeter J, Örtqvist Å, Naucner P, Larsson S, Lepp T, Roth A. *Cost-effectiveness of pneumococcal vaccination for elderly in Sweden*. Vaccine 2020;38:4988-95
- IV. Wolff E, Widgren K, Scalia Tomba G, Roth A, Lepp T, Andersson S. *Cost-effectiveness of varicella and herpes zoster vaccination in Sweden, using a dynamic model*. Submitted manuscript
- V. Wolff E, Larsson S, Svensson M. *Willingness to pay for health improvements using stated preferences: prevention vs treatment*. Value in Health 2020;23:1384-1390

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ABBREVIATIONS

| | |
|------|---|
| CEA | Cost-Effectiveness Analysis |
| CV | Contingent Valuation |
| DAM | Decision Analytic Modelling |
| DSA | Deterministic Sensitivity Analysis |
| ICER | Incremental Cost-Effectiveness Ratio |
| PSA | Probabilistic Sensitivity Analysis |
| QALY | Quality-Adjusted Life Years |
| RCT | Randomized Controlled Trial |
| TLV | The Dental and Pharmaceutical Benefits Agency |

DEFINITIONS IN SHORT

| | |
|---------------|--|
| Antitoxin | An antibody that counteracts a toxin |
| Attenuated | Lessened or weakened |
| Herd immunity | Occurs when a large proportion of the community is immune to a disease, making the transmission of disease unlikely. The whole community thus becomes protected and not just those who are immune. |
| Immunity | The state of being unsusceptible to a particular disease |
| Incidence | Number of new cases of a disease in a population during a specific time |
| Inoculation | A way of producing immunity by introducing an infectious agent onto an abraded or absorptive skin surface |
| Pathogen | A virus or bacteria that can cause disease |
| Prevalence | Number of existing cases of a disease in a population during a specific time |
| Vaccination | Treatment with a vaccine to produce immunity against a disease |
| Vaccine | A substance that provides immunity against one or several diseases |

1 INTRODUCTION

1 INTRODUCTION

Vaccinations are one of the most influential interventions of modern-day life. Many severe diseases that in earlier days caused a significant burden of disease and premature deaths have, more or less, become extinct. Vaccinations have both a direct effect on the vaccinated individual, as well as an indirect effect in reducing the transmission of a disease.

Society, and the individuals living in it, have a great need for health and health care to function and grow, but the resources available are scarce. Labour, in terms of health care personnel, and time, facilities, equipment, capital, and knowledge are all limited resources. This indicates a need to prioritize among resources since when resources are allocated to one alternative intervention, they cannot be used elsewhere in the health care sector. Any prioritization should be made in a transparent matter, and economic evaluation is one framework that can facilitate transparent decision making in health care, but without delivering the values or ethics to guide difficult decisions (1).

The emergence of a new pandemic in 2020 that has affected practically every corner of the world, has emphasized the need for new and effective vaccines. The development of new vaccines occurs at a rapid pace, which has been accentuated during 2020 when several pharmaceutical companies have started human trials of vaccines against COVID-19 just a few months after the virus was discovered.

New vaccines that are developed and introduced on the health care market both target diseases that already are vaccine preventable and established in national vaccination programmes, as well as infectious diseases that previously were not vaccine preventable. The targeted diseases differ regarding the severity and the burden of disease, as well as geographical areas where the diseases spread. Newer vaccines often tend to have a higher dosage price than older vaccines. Since resources are scarce, only the vaccines that are good value for money should be implemented in vaccination programmes to gain the most possible health for the allocated resources. The value for money, i.e. the cost-effectiveness, is a necessary focus for implementation of newer vaccines in national vaccination programmes, in addition to other factors such as effectiveness and safety.

Preventive health interventions, like vaccinations, often means treating a large number of individuals to save some of those individuals from a possible future disease or undesired health state. Introducing a new vaccination strategy in a

national vaccination programme could also entail large spending in the immediate future, while the returns, in the form of less resource use in the health care sector and a healthier population, potentially occur many years later.

Since prevention targets possible future ill health, it may be less prioritized than the treatment of an already manifested disease, and thus fewer resources are allocated towards prevention. The overall objective of this thesis was to investigate the cost-effectiveness of vaccinations against infectious diseases and to assess the relative willingness to pay for prevention compared to treatment.

2 HEALTH ECONOMICS

2 HEALTH ECONOMICS

Health economics is a discipline within the field of economics that analyses the efficiency, effectiveness, and value in the production and the consumption of health, public health, and health care. Since society's resources, in terms of labour, time, facilities, equipment, and knowledge, are limited at the same time as the demand for health and health care is unlimited, there is a need to prioritize (2).

Economic evaluation is a tool used by health economists to find the most cost-effective intervention from a range of alternatives. The purpose of economic evaluation is to guide how available resources can be allocated to maximize health and to do so in a transparent way (1). When resources are allocated to one alternative health care intervention, the same resources cannot be used for other beneficial interventions. This indicates that the economic cost of a health care intervention is not the direct budgetary outlays, i.e. the use of scarce health care resources, but rather the value of the foregone benefits that could have been achieved given an alternative intervention. This is referred to as *opportunity costs* (2).

Cost-effectiveness is the theoretical concept that dominates economic evaluation. The term can either refer to a desire to reach a predetermined health level at the lowest cost possible or to maximize health from a limited amount of resources (1). If an intervention or pharmaceutical treatment is deemed cost-effective, that means that the cost is considered reasonable in relation to its health effects. However, if the cost is reasonable or not depends on the cost-effectiveness threshold of a particular country, society, or setting.

There is no official threshold in Sweden. The applied threshold of cost-effectiveness analyses in Sweden is instead often assumed given national guidelines of what could be considered cost-effective (3), or deduced from earlier decisions from the Dental and Pharmaceutical Agency in Sweden (TLV) (4). Not only is an official threshold lacking, no guidelines link a threshold for treatment to that of prevention or vaccination. Since there are several characteristics of vaccination that distinguish it from treatment, there are reasons to investigate what the relative willingness to pay is of prevention compared to treatment.

2.1 ECONOMIC EVALUATION

Economic evaluation seeks to answer the question of whether the expected benefits of an intervention are worth the resources spent, or if the scarce resources instead should be allocated elsewhere. The first economic evaluations of vaccination programmes were reported in the literature in the 1970s (5).

The instrument used in health economics to assess the health benefits in relation to the economic costs is referred to as economic evaluation. Economic evaluation is a tool for decision makers when deciding on the implementation of new treatments and preventive interventions, and to make informed decisions on the allocation of health care resources under conditions of uncertainty (2). Economic evaluation deals both with the inputs and outcomes of interventions; the inputs are often referred to as costs and outcomes as consequences on health. The purpose of an economic evaluation is to identify, measure, and compare the costs and consequences of alternative actions (2) and helps to fill the gaps in evidence concerning public health effects on a population level. It can also inform decisions to disinvest from older interventions when there are new and more cost-effective alternatives (6).

Priorities should ideally be set in an organized manner, since basing a decision on a “gut feeling” or an “educated guess” is not likely to produce transparent and consistent results (2). The ethical platform in Sweden, which was adopted by the government’s proposition *Priorities in health care* (prop 1996/61:60) in 1996, states that prioritization within the health care sector should be made with respect to three principles (7). The three principles are:

- *The principle of human dignity* –all people have equal value and the same rights regardless of personal characteristics and functions in society,
- *The principle of need or solidarity* –resources should be invested in the areas where needs are the greatest, and
- *The principle of cost-effectiveness* – there should be a reasonable relation between costs and effects, measured through improved health or improved quality of life.

In Sweden, cost-effectiveness is one of three criteria that have to be fulfilled for vaccination against a disease to be included in a national vaccination programme. But how do we assess cost-effectiveness before a vaccine is introduced and before we have observed its impact in the real world? Since vaccinations prevent future bad health, relying solely on randomized

controlled trials (RCT) could have several limitations. For instance, the time horizon may not be sufficiently long to capture all the relevant health effects and costs of a new vaccine or vaccination strategy, or it may be ethically questionable to continue with an RCT. Under the conditions of uncertainty linked to the potential future effects, we cannot await the factual effect of a vaccine on the population level, and there is a need for another framework for decision making as a complement to an RCT. This framework is provided by decision analytic modelling (DAM), which can combine different sources of information, such as registry studies, cohort-studies, and RCTs. Guidance drawn from DAM is only as good as the quality of the model used – if the data are flawed, so will the decision making be (8). Guidelines regarding DAM suggest that before constructing a model, the scope and objective of the project and the target population should be identified. The justification for choosing a model type, time horizon, and the health states of the model should also be identified beforehand to make sure that the choice of modelling approach is an informed decision and not based on what model is easily available (2).

An economic evaluation should be transparent, and make sure that the underlying assumptions have been made explicit and that the context and perspective of the evaluation are adequately described, to enable validation. The purpose of economic evaluation is to inform decision makers on health care allocations, but it is also important not to only generate precise point-estimates for a specific outcome, but also to present the uncertainty surrounding those estimates (9). Two different concepts of uncertainty are important in decision analytical modelling and economic evaluation; *parameter uncertainty*, which refers to uncertainty in the parameter values, and *structural uncertainty*, which refers to uncertainty arising from the assumptions in the decision model. Parameter uncertainty can be investigated via sensitivity analyses varying the ingoing parameters, and structural uncertainty can be investigated via validation and calibration of the model.

Vaccination has two distinctive features compared to other health interventions. These features are common to preventive interventions as opposed to treatment. Firstly, there is often a delay between when the vaccine is administrated and the costs occur, and the time when the disease is averted, as in studies I and IV. However, this is not always the case, as in studies II and III, where the health effect occurs close after the vaccine is administrated. Secondly, vaccination against infectious diseases does not only reduce the risk of disease for the individual who is vaccinated but could also lead to an indirect protection in the unvaccinated population via herd immunity. Capturing the effect of herd immunity in cost-effectiveness analyses often requires multiple cohort models with long time horizons (10).

It is important to highlight that even though health economic evaluation provides important information to decision makers, it only focuses on one dimension of health care decisions. Therefore, health economic evaluation is of most appropriate use for decision making when combined with other decision making information – such as ethical and humanitarian considerations – for instance, equality in health, differences in needs, and access to health care (1, 2).

2.2 COST-EFFECTIVENESS ANALYSIS

It is common to distinguish between different economic evaluations, such as cost-benefit analysis (CBA), cost-minimization analysis (CMA), and cost-effectiveness analysis (CEA), which is sometimes referred to as cost-utility analysis (CUA). The different approaches all measure costs in monetary terms, whereas they differ in the measurement of benefits (1). The chosen approach depends on the issue under consideration and available data.

A cost-benefit analysis (CBA) measures both costs and benefits in monetary terms, and investigates if the benefits of an intervention outweigh the costs, and if so, by how much. Cost-minimization (CMA) analysis is a version of cost-effectiveness analysis, where two interventions are assessed to have the same health effects but at different costs. The intervention with the lowest costs is then considered to be the more cost-effective.

The most common approach in health care and public health policy contexts is cost-effectiveness analysis (CEA), which evaluates to what extent an intervention provides value for money, i.e. if the costs of an intervention (a new drug, treatment, medical device, etc.) are reasonable in relation to its effect. A CEA compares a new intervention with existing relevant interventions, standard of care, or a do-nothing-alternative (11). Cost-effectiveness is a relative concept – an intervention can never be cost-effective in itself, but always in relation to another intervention.

A CEA measures benefits in terms of health. It could measure only one dimension of health as, for instance, the number of avoided heart attacks as the result of an intervention. The drawback of such a measurement, however, is that it cannot be used to compare or prioritize interventions in different therapeutic areas: how do you value a prevented heart attack in relation to one year without pain for a person with rheumatism? To compare interventions in different therapeutic areas, one could instead use quality-adjusted life years (QALY), which combines two dimensions of health; health-related quality of

life and length of life. The QALY measurement is further presented in section 2.2.2.

The results from a cost-effectiveness analysis are often presented as an incremental cost-effectiveness ratio (ICER) (1), where the difference in costs is divided by the difference in health effects between the investigated intervention and the comparator (Equation 1). An ICER can be interpreted as cost per gained QALY (if health effects are measured in QALY), i.e. the cost for society to gain one year of full health.

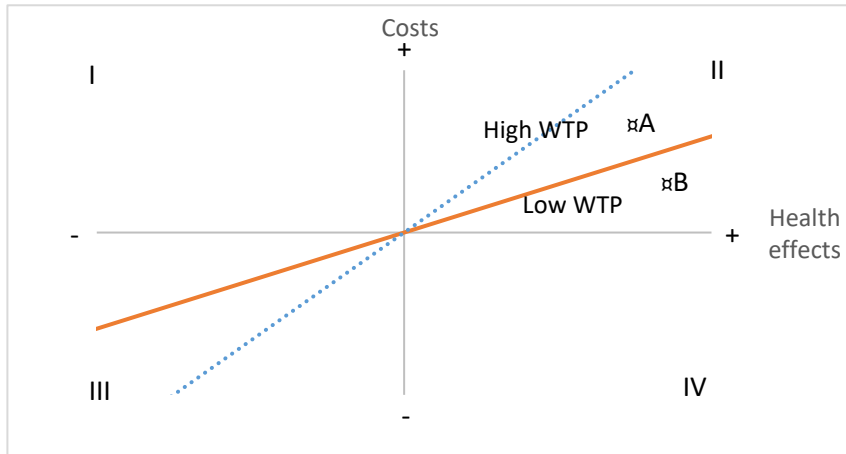
Equation 1

$$ICER = \frac{Cost_1 - Cost_0}{Effectiveness_1 - Effectiveness_0}$$

Where 1: new treatment, and 0: comparator.

Depending on the willingness to pay, this ICER could be deemed either cost-effective or not cost-effective. This is illustrated in Figure 1 that shows the cost-effectiveness plane, where increased or decreased costs and health effects of the evaluated interventions in comparison to the alternative intervention are measured on the y-axis and the x-axis, respectively.

Figure 1 Illustration of the cost-effectiveness plane



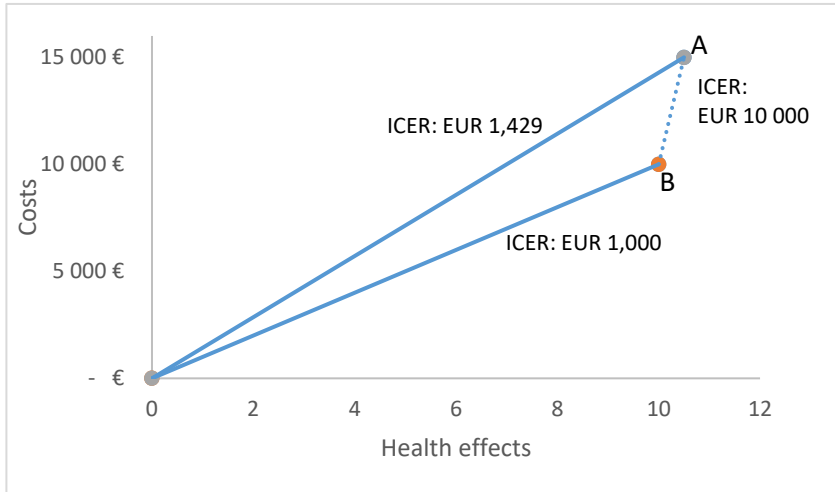
WTP = willingness to pay

Interventions that end up in the upper-left quadrant (I) are deemed not cost-effective or *dominated* since they have a higher cost and poorer health effect than the alternative intervention. In the lower-right quadrant (IV), an

intervention is always considered cost-effective since it is *dominating* the alternative intervention, i.e. has a better health effect at a lower cost.

In the upper-right (II) and the lower-left quadrant (III), the interpretation is less straightforward. An intervention that ends up in the upper-right quadrant has a better health effect but at a higher cost, and the cost-effectiveness thus depends on the willingness to pay (WTP) for the intervention. For instance, intervention A would be cost-effective with the high WTP (the dotted line) but not with the low WTP (solid line), whereas intervention B would be cost-effective with both the high and the low WTP. Threshold values are further discussed in section 2.3. In the lower-left quadrant (III), the intervention has a lower cost than the alternative intervention but a poorer health effect, and the interpretation is thus hard – how much health are we willing to give up to save money?

Often there is more than one alternative intervention to consider in a cost-effectiveness analysis, indicating that there will be multiple ICERs to calculate (12). To have a meaningful comparison, the costs and health effects that one intervention imposes over another must be examined, by using an incremental approach in cost-effectiveness analyses (2). An intervention is thus compared to each alternative intervention individually in the CEA (11). This is illustrated in Figure 2, where the competing intervention alternatives A and B are plotted together with their associated increased costs and health effects, compared to no intervention. Intervention A results in an increased cost of EUR 15,000 and 10.5 health effects. The corresponding costs and health effect for treatment B are EUR 10,000 and 10 health effects. The slope of the curves represents the cost per gained health effect of each treatment alternative (ICER, treatment A: EUR 1,429; ICER, treatment B: EUR 1,000). However, since treatment A and treatment B are independent and competing, the costs and health effects of the alternative interventions must be compared to each other. As such, we want to investigate what the costs are for the extra health effects that intervention A gains over intervention B. The dotted line represents the cost per gained health effect for treatment B compared to treatment A (ICER: EUR 10,000). The slope is much steeper than the other two lines, indicating a higher cost per gained health effect.

Figure 2 Illustration of an incremental cost-effectiveness analysis

The next two sections describe how the two components of a CEA is measured and quantified: costs and QALY.

2.2.1 COST ANALYSIS

A cost analysis defines and identifies, measures, and values the costs of an illness or an intervention (13). Costs are estimated by quantifying the different types of resource use for treating an illness and then multiplying these by their unit cost.

What costs to include in a cost analysis depends on the perspective of the health economic evaluation; a societal perspective includes all costs and health effects, regardless of who incurs the costs and whom the costs affect (14). A health care perspective includes costs within the health care sector and costs borne by third-party payers and out-of-pocket payments for patients (6). It is essential to decide the perspective of the evaluation and to specify which costs are to be included in the analysis and which are not, to make sure that the results cannot be misinterpreted. Table 1 presents cost components that can be included using a health care perspective and a societal perspective, respectively.

Table 1 Cost components included in the health care perspective and the societal perspective

| Cost Component | Health Care Perspective | Societal Perspective |
|--|-------------------------|----------------------|
| Resource use in the health care sector | Yes | Yes |
| Intervention costs | Yes | Yes |
| Logistics costs* | Yes | Yes |
| Production loss | No | Yes |
| Cost of informal care** | No | Yes |

* e.g. the cost of storing vaccine doses, ** unpaid care for a dependent care-taker from e.g. a spouse or child

Health care costs include the resources used within hospitals, transportation to hospitals, out-of-pocket expenditures for patients, and health services in other sectors. Non-health care costs in the form of production loss are the value of production forgone to society when a patient is unable to work (15). Production losses can only be incurred when an individual is of working age, i.e. not for children or retired individuals. For children, however, the production loss among parents when a child is ill can be quantified and included in an economic evaluation. In Sweden, the Dental and Pharmaceutical Benefits Agency (TLV) recommends production loss to be quantified by the human capital approach (16). That is, production shortfalls are valued at the market price, i.e. wage estimates, of the goods and services that otherwise would have been produced. TLV also recommends that the results from a health economic evaluation are presented both with and without including production losses (6, 16).

As mentioned earlier, cost consists of two elements, the quantity of resources and the price of resources. The quantity of resources often depends on the data of the evaluation – if collected during a randomized controlled trial, the quantity of resource use may be collected from the case report forms. In other situations, the quantity of resource use must be estimated by experts, via national guidelines or hospital records, for instance. In theory, the proper price for a resource is its opportunity cost, i.e. the value of forgone benefits, but a more pragmatic approach is to use its market price, which is considered a useful approximation of opportunity cost (2).

Since health economic evaluation compares costs and effects between two or more interventions, costs common to all interventions can be omitted since they will not affect the choice of interventions (2). In addition, it may not be worth the time to consider costs that are small and unlikely to make any

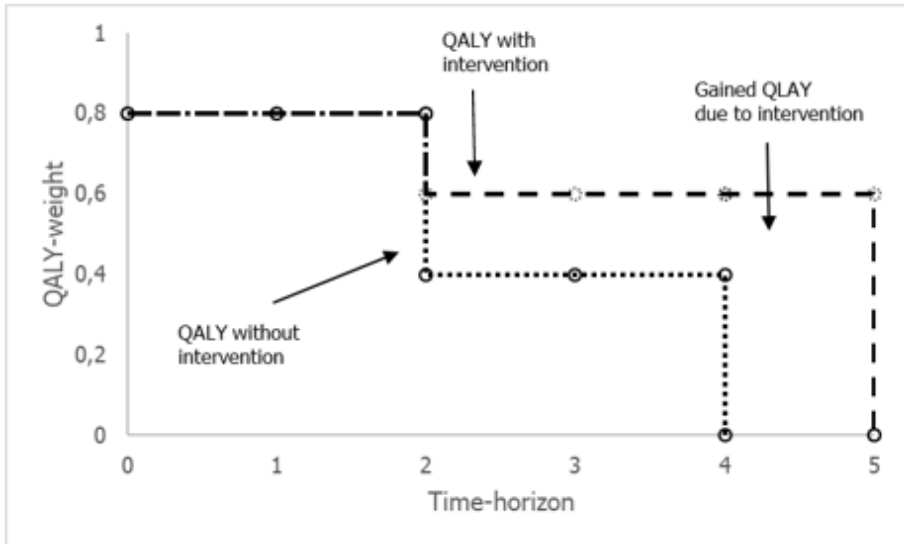
difference in the results, but an elimination of such costs should always be justified and documented.

2.2.2 QUALITY-ADJUSTED LIFE YEARS (QALY)

Quality-adjusted life years (QALY) is commonly recommended as the health effect measurement in health economic evaluations (6, 16). QALY was first introduced in 1968 by Klarman et al (17) and is a combination of two dimensions of health: the quality of life, and the length of life. QALY is a generic measure that enables the comparison of interventions between different therapeutic areas, in contrast to disease-specific measures that only allow for comparisons within the same therapeutic area.

To gain accumulated QALY over a set time horizon in a health economic evaluation, QALY-weights are needed to represent the quality of life in the investigated health states. A QALY-weight must be based on preferences, anchored at perfect health and death, and be measured on an interval scale (2). The preference-based part of the QALY indicates that a more desirable, i.e. a more preferred, health state should be valued higher in the analysis. To define an interval scale of QALY-weights, perfect health and death can be given arbitrary values as long as the value for death is lower than the value for perfect health, but often the scale is anchored at 0 and 1 (0=death, 1=perfect health) (2). When the value of one is used as the value for “perfect health”, then QALY can be noted as “years lived in perfect health”.

A QALY is constructed by multiplying one life year lived with the QALY-weight during that life year. An individual who lives one year in perfect health (QALY-weight of 1) has the equivalent of one QALY, whilst an individual who lives one year with only 60% of perfect health (QALY-weight of 0.6) has the equivalent of 0.6 QALY. This is illustrated in Figure 3, where the number of QALY is the area under the curve generated with and without an intervention over a time horizon of five years. The number of QALY without intervention sums to 2.4 and the equivalent number with intervention sums to 3.4, indicating that, with the intervention, one year of perfect health is gained over the five-year time horizon.

Figure 3 An illustration of the calculation of QALY

There are direct and indirect methods to elicit QALY-weights. The direct methods include time trade-off, standard gamble, and rating scales. The time trade-off method presents the individual with two options; either living 10 years in the current health state or a shorter time in perfect health. The time in perfect health is varied until the individual is indifferent between the two options. If the individual is, for instance, willing to trade off four out of the offered ten years to regain full health, this indicates that six years in full health is equivalent to 10 years in the individual's current health states and thus a QALY-weight of 0.6. The standard gamble method introduces risk in the decision making for the individual. The individual is again presented with two options, this time between remaining in the current health state with certainty, or taking a gamble of either gaining full health or dying (with some probability of death p). The probability of death is then varied until the individual is indifferent between remaining in the current health state with certainty and the gamble. One minus the probability of death ($1-p$) where the individual is indifferent is interpreted as the valuation of the current health state in relation to perfect health, i.e. the QALY-weight (18). With rating scales, such as the visual analogue scale, the respondent is asked to indicate where on a scale with two endpoints – one being perfect health and one being worst possible health, their current perceived health state is. The scale often ranges from 0 to 100 (18).

Since it can be difficult and time-consuming to measure QALY-weights with the methods described above, indirect elicitation methods have been

developed. These include pre-scored generic preference-based measures, which are often used in health care trials. There is a range of generic preference-based measures, including the EuroQol EQ-5D, the Short Form 6D (SF-6D), and the Health Utilities Index (HUI). EQ-5D is a commonly used instrument in CEA and consists of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each health state has been weighted using mostly TTO in large population-studies conducted in several countries, including Sweden (19-21).

Even though the QALY is established as the leading health effect measurement in cost-effectiveness analyses, there are limitations to its application, and several issues have been raised, both ethical and methodological, as well as context-specific (22). The QALY measurement has also been critiqued for not being sensitive enough to small but clinically meaningful changes in health, which could be very important in certain sub-populations.

2.3 THRESHOLD VALUE

Even though cost-effectiveness has a long tradition of informing health care decision making, there is no official threshold in Sweden stating when an intervention is considered cost-effective or not, in contrast to e.g. the UK and Ireland (23). The National Board of Health and Welfare has, in their national recommendations, provided guidelines for how to assess when a cost per gained QALY can be considered low, moderate, high, or very high (3) (see Table 2). The “optimal” threshold may vary both between therapeutic and geographical areas (24), and there are no guidelines on whether the threshold should differ between different categories of interventions, for instance between preventive interventions, such as vaccinations, and treatments.

Previous studies show that the willingness to pay (WTP) for intervention varies with the severity of disease and the need for interventions (4, 25-27). The studies suggest that WTP increases with severity and that a higher ICER more often is considered cost-effective if the patient group lacks other treatment options. In England, there is also evidence that the NHS uses different WTP depending on if the intervention is end of life treatment or not (28). Gyrd-Hansen (29) points out that it is likely that time preferences and time horizons for health improvements will influence WTP for health.

Table 2 Guidelines on the interpretation of cost per gained QALY (3)

| Cost per gained QALY | Interpretation |
|-----------------------|----------------|
| >100,000 SEK | Low |
| 100,000-500,000 SEK | Moderate |
| 500,000-1,000,000 SEK | High |
| <1,000,000 SEK | Very high |

There are two perspectives of what the threshold of cost-effectiveness ought to represent (30):

- *Demand-side*: the society's valuation of a QALY
- *Supply-side*: the opportunity costs of the cost per gained QALY of the displaced intervention

The demand-side approach requires the knowledge of society's WTP for health improvements to determine the threshold. The marginal WTP can be elicited via revealed or stated preference methods and contingent valuation studies (see section 5.2). Interventions with a cost per gained QALY below the society's WTP are deemed cost-effective. The demand-side approach is detached from the budget and instead assumes a dynamic budget (31).

The supply-side approach, focusing on opportunity costs, is based on the idea that new treatments impose an additional cost on the health care system (30). The displacement of existing treatments might be required, which could result in health decreases elsewhere in the system. The threshold should therefore represent the cost per gained QALY of the displaced treatments, which allows for the assessment of whether health gains from the new treatment exceed the health gains that are expected to be forgone by the displaced treatment (32).

A study of the impact of the cost per gained QALY and severity of disease on reimbursement decisions from the Dental and Pharmaceutical Benefits Agency (TLV) found that the likelihood of approval was 50/50 at a cost per gained QALY of 700,000 SEK for a non-severe health-state and 1,000,000 SEK for a severe health-state. When the cost per gained QALY was as high as 1,000,000 SEK for the non-severe states, and 1,250,000 SEK for the severe states, the probability of reimbursement approval was very low (3-4%) (4).

In a study by Siverskog and Henriksson from 2019 (33), the authors sought to estimate the marginal cost of a life year in Sweden's public health care system. The study found that the marginal cost per life-year was about SEK 370,000, and that the marginal cost per QALY was between SEK 180,000 and SEK

430,000. If we assume the lower marginal cost per QALY, the results suggest that for SEK 1,000,000, we can produce approximately five QALY in Sweden.

3 VACCINATION

3 VACCINATION

There are two types of immunity: *active* and *passive*. Active immunity is a result of exposure to a pathogen that triggers the immune system to produce antibodies. Active immunity is often long-lasting, or even life-long, but it usually takes several weeks to develop it. Exposure to the disease organism occurs either through infection with the disease, which results in *natural immunity* or through the introduction of a killed or weakened form of the disease organism through vaccination, which results in *vaccine-induced immunity* (34). Passive immunity occurs when an individual is given antibodies to a disease instead of producing them through their immune system. Passive immunity is immediate. For instance, passive immunity can be acquired by a newborn baby from its mother through the placenta, or when antibodies are given as medication to a nonimmune patient. In this thesis, the term “vaccination” is used as a form of primary prevention, i.e. to prevent a disease before it occurs, and not as post-infection prophylaxis or passive vaccination.

Vaccination and the implementation of vaccination programmes are of utmost importance to public health. Second to clean water, vaccinations are the most efficient way to promote health and to save lives, in high as well as in low-income countries. Not even antibiotics have had such a major impact on the reduction in mortality and morbidity and on population growth as vaccinations (35). Many severe diseases that in earlier days caused a significant burden of disease and premature deaths have become extremely rare in Sweden, thanks to vaccination programmes with high coverage.

Even though the greatest progress in the field was primarily seen during the 20th century, immunization has a very long history. The Chinese used inoculation (i.e. adding the infective agent onto an absorptive skin surface) to protect individuals from smallpox as early as 1000 CE, and Indian Buddhists drank snake venom to become immune already in the 7th century (35). Before being introduced to Europe and the Americas, inoculation was practised in Africa and Turkey as well (36). Edward Jenner inoculated patients with cowpox to create immunity to smallpox in 1796 and made the practice widespread. This resulted in the eradication of smallpox some 200 years later (35). The next vaccination that had an impact on human disease was the rabies vaccine, invented by Louis Pasteur in 1885. As bacteriology developed, new antitoxins and vaccines came in place. At the beginning of the 20th century, there were five vaccines in use: smallpox and rabies vaccine, as well as vaccines against typhoid, cholera, and plague. It was also a common and accepted practice to immunize with diphtheria and tetanus antitoxin at this time

(35). The mid-20th century was an active era for vaccination research and development, and vaccines that greatly reduced the disease burden became available for polio, measles, mumps, and rubella.

Vaccines are made by using several different processes and induce protection against infectious diseases in different ways (35) and have generally proven to be safe. The technological advancements in recent years makes even safer vaccines possible (37).

Today, there are five types of vaccines that are routinely given within the national vaccination programme in Sweden. *Live attenuated vaccines* introduce a weaker form of the pathogen into the body and results in asymptomatic infection. Since the bacteria or virus is weakened, it will not cause illness but the immune system will learn to recognize the pathogen and know how to battle it when coming in contact with it. Live attenuated vaccines can result in lifelong immunity with just one or two doses, but cannot be given to immunosuppressed individuals (38). Examples of live attenuated vaccines are the MMR vaccine (measles, mumps, and rubella), as well as the rotavirus, and varicella vaccines.

In *inactivated vaccines*, such as the polio vaccine (38), the pathogen is killed and the dead cells of the pathogen are introduced into the body. The immune system learns how to fight the disease, even though the pathogen is dead. The inactivated vaccines are often safer, since there is no risk that the pathogen will mutate into its disease-causing form, but since it is dead, it often takes many booster-doses to maintain protection.

For some diseases, it is possible to isolate a specific protein or carbohydrate from the pathogen that can stimulate and train the immune system when it is injected into the body, without provoking illness. Those vaccines are called *subunit/conjugate vaccines* and are used for diseases such as human papillomavirus (HPV), pneumococcal disease, influenza, and the pertussis component of the DTaP vaccine (38). Since only a part of the pathogen is injected into the body, the risk of adverse events is low, but only some vaccines can be produced in this way, since it is not always possible to isolate a protein or carbohydrate from the pathogen.

Toxoid vaccines, used against bacterial diseases that inflict damage by secreting toxins, such as diphtheria, and tetanus, are produced by deactivating the toxin and then injecting it into the body. The immune system then learns from the dead toxins how to fight off living toxins. *Conjugate vaccines*, such as the vaccine against the bacterial disease *Haemophilus Influenzae* Type B

(Hib) have an outer coating of sugar molecules to camouflage its antigens and are created by linking an antigen from another, recognizable, pathogen to the camouflaged bacteria. The immune system thus learns that the sugary camouflage itself is harmful and then attacks the bacteria when it attempts to enter the body.

Other types of vaccines, still in their experimental stages, are *DNA vaccines* and *RNA vaccines*. DNA vaccines consist of the pathogen's DNA, which instructs the immune system to produce antigens to fight the pathogen. *RNA vaccines* consist of an mRNA strand that is coded for a disease-specific antigen – when the vaccine is inside the body's cell, the sequence is translated to produce the encoded antigens, which stimulate the immune system to produce antibodies. Finally, *recombinant vector vaccines* are a form of weakened DNA vaccines (39). Both DNA and RNA vaccines have generated significant interest due to their potential to avert disease, but also because they can be produced quickly with fairly generic manufacturing processes (40). With recombinant DNA technology and new delivery methods, innovative techniques are driving vaccine research and the number of diseases possible to target with immunization is growing (36).

Besides the direct effect of vaccination, i.e. the averted disease for the vaccinated individual, and the effect on society from the reduced burden of disease – both concerning resource use in the health care sector and the quality of life of the population – there are indirect effects of vaccination. One of the most important indirect effects of vaccinations is herd immunity, which emerges in a population when a large proportion of the population has become immune to an infectious disease (41). Since immune individuals cannot contribute to the transmission of the disease, herd immunity protects those who are not vaccinated or immune. Other externalities can emerge as a consequence of vaccination. Serotype replacement or the impact of vaccination on antibiotic resistance are two examples (41). Serotype replacement is defined as an increase in non-vaccine-type serotypes when a vaccine is in place.

3.1 THE SWEDISH VACCINATION PROGRAMME

Since 2013, national vaccination programmes in Sweden are regulated by the Communicable Disease Act (42). The government decides what diseases are included in the national vaccination programmes, based on recommendations from the Public Health Agency of Sweden.

For a disease to be included in a national vaccination programme, the vaccination targeting the disease must fulfil three criteria that are regulated in the Communicable Disease act, namely:

- 1) Reduce transmission and burden of disease
- 2) Be cost-effective
- 3) Be ethical from a humanitarian standpoint

The second criterion of cost-effectiveness implies that the vaccination programme should have reasonable costs in relation to its health benefits.

The Swedish national vaccination programmes are divided into two different segments; general and specific vaccination programmes. As of 2020, there is only one general vaccination programme in place in Sweden; *the national vaccination programme for children*. The general vaccination programme for children includes eleven diseases: rotavirus, polio, diphtheria, tetanus, pertussis (whooping cough), invasive infections with Haemophilus Influenzae type b (Hib), pneumococcal disease, and measles, mumps, rubella (MMR), and human papillomavirus (HPV) (see Table 3) (43). Up until the fall of 2020, HPV vaccination was only given to girls in Sweden, but from the fall of 2020, it is also given to boys within the national vaccination programme.

Table 3 The national vaccination programme for children in Sweden

| Age | 6 weeks | 3 months | 5 months | 12 months | 18 months | 5 years | | | |
|----------------------|---------|----------|----------|-----------|-----------|---------|--------|----------|--------|
| Grade | | | | | | | 1-2 | 5-6 | 8-9 |
| Rotavirus | Dose 1 | Dose 2 | Dose 3* | | | | | | |
| Diphtheria | | | | | | | | | |
| Tetanus | | | | | | | | | Dose 5 |
| Pertussis | | Dose 1 | Dose 2 | Dose 3 | | Dose 4 | | | |
| Polio | | | | | | | | | |
| Hib | | | | | | | | | |
| Pneumococcal disease | | Dose 1 | Dose 2 | Dose 3 | | | | | |
| Measles | | | | | | | | | |
| Mumps | | | | | Dose 1 | | Dose 2 | | |
| Rubella | | | | | | | | | |
| HPV | | | | | | | | Dose 1+2 | |

*if vaccine given in three doses

The vaccination coverage in the national vaccination programme for children is high in Sweden. Among children born in 2015, more than 97% had at least three doses of diphtheria, tetanus, pertussis, and Hib, and approximately 97%

of the children were vaccinated with three doses of the MMR-vaccine. The figures are somewhat lower for the HPV vaccination, where the vaccination coverage with at least one dose among girls born in 2002, 2003, and 2005 was 82%, among girls born in 2004 it was 80%, and among girls born in 2006, it was 84% (43).

The government has not yet decided upon any specific vaccination programmes for risk groups, but the Public Health Agency of Sweden has suggested introducing vaccination programmes against four diseases: hepatitis B, seasonal influenza, pneumococcal disease, and tuberculosis. The groups that would be targeted in the specific vaccination programmes are at greater risk of contracting the disease (e.g. people who inject drugs and hepatitis B) or at greater risk of severe illness if they contract the disease (e.g. elderly and seasonal influenza).

Regions and municipalities in Sweden are obliged to offer its population vaccinations included in a national vaccination programme free of charge for the individual and to register vaccinations in the national vaccination registry. In addition to the national vaccination programmes, the Public Health Agency can issue recommendations on vaccinations. The recommendations are not binding, and the regions can decide whether or not to follow the recommendations, how and if they should be implemented, and any out-of-pocket payments for the individual.

3.2 VACCINE PREVENTABLE DISEASES

In this section, the four infectious diseases that were evaluated regarding their potential cost-effectiveness of vaccination in Study I through IV are presented: human papillomavirus, pertussis (whooping cough), pneumococcal disease, and varicella-zoster virus (varicella and herpes zoster) together with burden of disease, associated vaccination strategies, and target groups.

3.2.1 HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) is the most commonly sexually transmitted infection among both men and women. More than 200 HPV-types have been identified, of which 40 types are known to be sexually transmitted (44). About 90% of HPV infections are cleared within one to two years, but some infections persist and can cause a range of HPV-related health states including anogenital warts, precancerous lesions, and cancer (45).

Thirteen high-risk HPV-types are known to cause cervical cancer. Those thirteen types also contribute to cancer in the anogenital region, such as cancer of the vagina, vulva, anus, and penis as well as in the oropharynx, mainly tonsillar and base of tongue cancer (46, 47). HPV 16 and 18 are the dominating causes of cervical and non-cervical HPV-related cancer (46, 48). All three of the available vaccines specifically target HPV 16 and 18.

Oropharyngeal cancer, which mainly occurs among men, has increased rapidly in western countries over the last few years (49-53). Today, oropharyngeal cancer the second most common head and neck cancer in Sweden with 384 new cases diagnosed in 2015, 71% among men (54, 55). Around 100 men are diagnosed with invasive penile cancer annually (56). Around 150 individuals are diagnosed with anal cancer annually in Sweden, 30% among men (57).

Since Sweden started to offer HPV vaccination to girls within the national vaccination programme in 2012, a reduction in HPV infections (58), cervical intraepithelial neoplasia (CIN) (59), and genital warts (60) have been observed among women. Clear herd immunity effects have also been demonstrated, both for women and men, in countries with vaccination programmes for girls, (61) or sex-neutral vaccination programmes (62, 63). In a recent study, the effect of HPV-vaccination on cervical cancer in Sweden was demonstrated (64), and the effect on cancer has also been shown in one of the major HPV vaccine trials (65). Few countries have implemented sex-neutral vaccination programmes against HPV, and some countries have instead implemented risk-group vaccination programmes offering HPV vaccination to men who have sex with men, for instance, the UK and Ireland.

The mean national vaccination coverage among girls in Sweden has been around 80% for one dose since the beginning of the programme in 2012 (66). Increasing the uptake among girls could have a greater impact on the burden of HPV-related disease than introducing vaccination also for boys (67, 68). However, increasing the coverage among girls in a setting where the coverage is already high may be more challenging than to vaccinate a moderate proportion of boys. Since the fall of 2020, Sweden has a sex-neutral HPV vaccination programme.

3.2.2 PERTUSSIS (WHOPPING COUGH)

Pertussis, or whooping cough, is caused by the *Bordetella Pertussis* bacteria and is a drawn-out and highly contagious respiratory infection (69). Infants suffer the most severe complications and are more likely to be hospitalized

than older children and adults (70-74). The infection could be severe in incompletely or unvaccinated infants less than twelve months old.

Pertussis is resurgent universally (75) and many European countries with high vaccination coverage have observed re-emergence of pertussis. The increase in incidence implies that there is a need for improved and alternative vaccination strategies to protect infants from pertussis (76, 77). Consequently, the UK and the USA have implemented new vaccination strategies against pertussis (78, 79), such as vaccinating adults in close contact with infants that are too young to be fully immunized, (i.e. the “cocooning strategy”) and vaccinating pregnant women. These vaccination strategies aim to transfer antibodies from the mother to the child at birth and to protect the infant when he or she is the most vulnerable.

In enhanced surveillance in 2014, 688 cases of pertussis were reported in Sweden (80). This is more than a threefold increase compared to 2013 (223 cases), and the increase was reported in the majority of age groups. Infants had the highest incidence, and the majority of the infants (103 of 121 cases, 85%) had pertussis before the age of five months, i.e. before they were fully vaccinated against pertussis. Eleven children died during 1996-2013, of which ten were younger than 6 months. In 2014, two children died, both younger than 3 months and unvaccinated.

3.2.3 PNEUMOCOCCAL DISEASE

The bacteria *Streptococcus pneumoniae* bacteria is one of the most common causes of community-acquired pneumonia (CAP) and can also give rise to invasive pneumococcal disease (IPD). Severe disease from pneumococcal infections among adults is significant. This is especially true in older age groups, and among individuals with certain underlying diseases, and despite the substantial positive indirect effects of general childhood vaccination programmes with pneumococcal conjugate vaccines (PCV) (81-83).

A study from 2019 (84) found that the incidence of CAP, both inpatient and outpatient, among 65 year-olds was about 2,400 annually. The corresponding figure for 75 year-olds was about 3,800. However, not all CAP is preventable with pneumococcal vaccination. The average number of annual IPD cases in Sweden from 2014 to 2018 was 32 for 65 year-olds and 43 for 75 year-olds (80).

The significant decline in the incidence of infections that have been observed in all age groups in many countries due to the serotypes of the conjugate vaccine has been largely counteracted in adults by an increase of non-vaccine

serotypes (82, 85, 86). The usefulness of the PCV vaccine in adults is limited due to an increase in pneumococcal disease caused by serotypes that are included in the 23-valent polysaccharide vaccine (PPV23), but not in the 13-valent conjugate vaccine, and of serotypes not included in either of the vaccines. As CAP incidence also increases dramatically with age, a general programme for all elderly, regardless of underlying disease, could be motivated. Pneumococcal vaccination for adults is not included in the national vaccination programme in Sweden, and despite official recommendations to vaccinate medical risk groups and all persons 65 years and older, the vaccination coverage is estimated to be low (84).

3.2.4 VARICELLA ZOSTER VIRUS

The *Varicella-zoster virus* (VZV) causes both varicella (chickenpox) and herpes zoster (shingles), where varicella is the clinical presentation of primary infection with the VZV. Varicella is extremely contagious and nearly everyone will contract the disease early in life. A study from 1997 showed that 98% of Swedish 12-year olds had VZV IgG antibodies, meaning that they had had varicella at some time point before that age (87). Varicella is usually mild in children and the symptoms in general last about one week (88). Complications can occur, and the risk of severe disease increases with age. Pregnant women risk a more severe disease than other adults, and varicella in early pregnancy can give rise to birth defects, so-called congenital varicella syndrome (88).

Effective vaccines against varicella have been available since the mid-1990s (89). Routine childhood vaccination programmes are in place in several countries worldwide (90, 91), where significant declines in varicella incidence after the introduction of the vaccine have been observed (91-94).

Following the primary varicella infection, the virus remains latent lifelong in the dorsal root and cranial ganglia. Many decades later, the virus can reactivate, which leads to herpes zoster. In the current Swedish situation, where nearly everyone has contracted varicella early in life, almost all adults are at risk of developing herpes zoster. The lifetime risk is estimated to be 25-30%, and as high as 50% in the age group 85 and older (95). The manifestation of herpes zoster is usually a unilateral vesicular rash in the skin area supplied by the affected nerve accompanied by itching, pain, and numbness. The pain may be intense and is described as burning or electric-like pain that usually resolves within 2 to 4 weeks, but complications of herpes zoster are relatively common, such as post-herpetic neuralgia.

4 AIM

4 AIM

The overall aim of this thesis was to investigate the cost-effectiveness of vaccination against infectious diseases in a Swedish setting. The evaluations differed greatly regarding the targeted pathogens and populations, indicating that different model types and time horizons needed to be applied. Additionally, the thesis aimed to investigate whether the willingness to pay differed between preventive interventions and treatment.

The aims of the included studies were as follows:

- I. To assess the cost-effectiveness of expanding the Swedish HPV-vaccination programme to include preadolescent boys, by comparing health effects and costs of HPV-related disease with a sex-neutral vaccination programme versus only vaccinating girls.
- II. To evaluate the potential cost-effectiveness of alternative vaccination strategies to protect infants against pertussis. Three alternative vaccination strategies were investigated: cocooning, maternal vaccination, and on-schedule vaccination.
- III. To assess the cost-effectiveness of including pneumococcal vaccination for the elderly in a national vaccination programme in Sweden, by comparing health effects and costs of pneumococcal-related diseases with a vaccination programme versus no vaccination.
- IV. To perform cost-effectiveness analyses of introducing varicella and/or herpes zoster vaccination in the Swedish national vaccination programme by assessing the health effects and costs of the programmes.
- V. To investigate whether there is a difference in willingness to pay between prevention and treatment for health improvements of equal magnitude.

5 METHODS AND DATA

5 METHODS AND DATA

This section describes the data and methods of the different studies of this thesis. Section 5.1 presents the methods and data for Studies I-IV, and section 5.2 further presents the method and data for Study V.

5.1 DECISION ANALYTIC MODELLING

Decision analytic modelling (DAM) is used to construct and structure decision making and includes several methods and tools to identify, clearly present, and assess a decision situation. DAM is used to present the options available for the decision maker, quantify the uncertainty in the decision, and evaluate alternative measures (13). As such, DAM satisfies five important objectives in the case of health economic evaluations, namely:

- *Structure* – provides a structure that reflects the possible health states that individuals may experience, and how interventions or treatments being evaluated impact these health states,
- *Evidence* – identifies the evidence relevant to the study question,
- *Evaluation* – provides means of translating the relevant evidence into estimates of health effects and costs,
- *Uncertainty, and variability* – facilitates the assessment of the uncertainty relating to the evaluation, and
- *Future research* – identifies prioritization of future research through the assessment of uncertainty (2).

Models and randomized controlled trials are best considered as complements, rather than substitutes since trials and other studies provide the evidence that is incorporated in decision models to address the decision problem. In short terms, in DAM, a model is developed to simulate the burden of disease in a population to examine whether an intervention is cost-effective in comparison to an alternative approach (96). The choice of comparator, i.e. the alternative approach, has a fundamental impact on the evaluation and should be clearly described, since it guides the interpretation of the results (97).

Table 4 presents the interventions investigated, the comparator, the target population, model-type, time horizon, and discount rate applied in Studies I through IV.

Table 4 Parameters included in the economic evaluations conducted in Studies I-IV

| Paper | Intervention | Comparator | Population | Model-type | Time horizon | Discount rate |
|-------|---|---|---|---|-----------------------|-----------------------|
| I | Sex-neutral HPV vaccination | Girls vaccination only | 2015 birth cohort in Sweden | Markov multistate model, dynamic | 100 years | 3% both cost and QALY |
| II | Pertussis vaccination 1. Cocooning 2. Maternal 3. On-schedule | 1. Today's vaccination programme 2. Incremental analyses | Average birth cohort 2004-2013, assuming two or one parent, in Sweden | Decision tree model, deterministic | One year | N/A |
| III | Pneumococcal vaccination 1. 65 year-olds 2. 75 year-olds | 1. No vaccination 2. Incremental analyses | 65-year-old cohort, and 75-year-old cohort, 2015, in Sweden | Single-cohort deterministic decision tree model | Five years | 3% both cost and QALY |
| IV | 1. Varicella vaccination 2. Herpes zoster vaccination 3. Both varicella and herpes zoster vaccination | 1. No vaccination 2. Incremental analyses | Population data, 2012, in Sweden | Dynamic transmission model | 85 years/ 20 years | 3% both cost and QALY |

5.1.1 MODEL CHOICE

The structure of the model was primarily determined by the epidemiology of the infectious disease that the vaccination programme targeted (11). Models are used to estimate the long-term effects of vaccination and vaccination programmes and need to be developed transparently, be easily accessible, and subject to precise validation processes (5). A vaccination programme may change the dynamics of a disease for the whole population, not just the vaccinated, which in some cases should be accounted for.

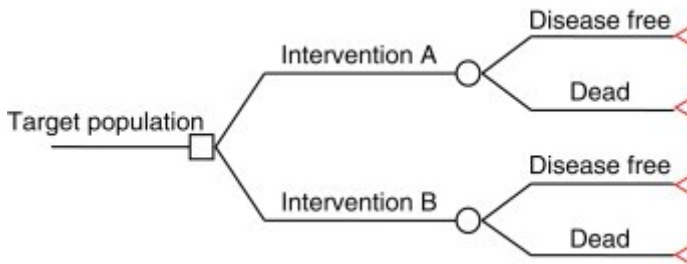
A model can be either cohort-based or population-based. In a cohort-based model, a group of individuals sharing the same characteristics during a defined period are modelled, and the individuals are often considered as being representative, or average, individuals. A population-based model intends to

reflect the demographic, epidemiological, and clinical characteristics of the target population (8, 11). A population design can be preferred when the changed in disease dynamics need to be captured, for instance, the herd immunity, since a cohort-based model does not capture all disease dynamics over time (11).

There are different types of mathematical models to be applied in a DAM, and different models are suitable in different settings. For instance, decision tree models are considered to be appropriate for short time horizons, whilst longer time horizons require the use of models with state transition, such as Markov models (96). The time horizon should last until steady state is achieved, i.e. when the epidemiological variation of a dynamic model ceases (11, 41).

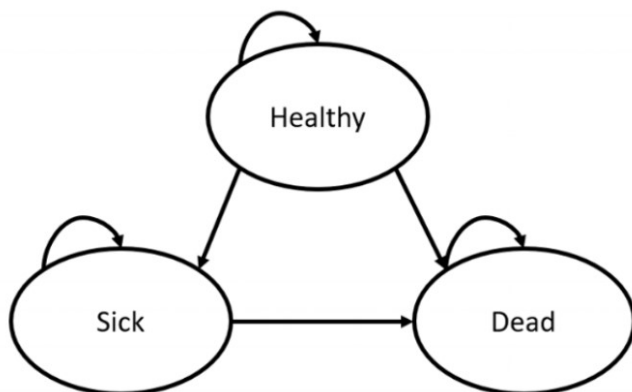
A decision tree model is the simplest structural model to be implemented in DAM (see Figure 4), where the outcomes of patients are visualized as a series of decision nodes following pathways of probabilities for each respective branch. Decision tree models are very useful for simple decision problems, but cannot model events that occur repeatedly or in a structural matter other than branching out the decision tree, since decision trees assume that all events occur instantaneously in the model.

Figure 4 Illustration of a decision tree model. Source (98)



Instead, one can use a Markov model (see Figure 5). Markov models are commonly used to provide a framework that represents sequences of events, where individuals in the model have different probabilities to transition from one state to another, depending on what state the patients are currently in and the time cycle of the model. Since transitions in the Markov models are dependent only on the current state, they are said to be “memory-less”. In addition, there are transmission models, that, instead of modelling health states, model the transmission of disease, which often are used in epidemiological modelling. However, such transmission can also be illustrated as a Markov model.

Figure 5 *Illustration of a Markov model*



Decision tree models and Markov models can be either deterministic, indicating that the input values are set deterministically and that base-case results and sensitivity analyses are fully replicable (41), or probabilistic with probability distribution applied to the input values. They can also be static or dynamic. Static models may be preferred when it is evident that omitting the dynamics of the disease will not lead to an underestimation of the intervention, either positively or negatively. A dynamic model, however, can account for the indirect effects of vaccination, such as herd immunity, which could play an important role in cost-effectiveness analyses of vaccination.

The models in Studies I through IV range from a simple static decision tree model with a one-year time horizon to a more complex dynamic Markov transmission model with a 100-year time horizon.

5.1.2 MODEL VALIDATION

The chosen level of complexity is important since a model that is too simple can lose validity and a model that is too complex can lose transparency. Alternative model structures can have an impact on the results and thus also on decision making, why it is important to validate the model. There are three key aspects to validate a model, namely: face validity, internal validity, and external validity (13).

Face validity entails investigating the assumptions, structure, and results from the model and if they are reliable, sensible, and intuitive. Internal validation, which also includes calibration of the model, relates to the logic of the model and if the inputs of the model relate to its outputs. For example, if all costs are

set to 0, the total costs should also be zero after running the model. The rationale is to make sure that the model behaves in the way it is supposed to. External validation concerns to what extent the model can predict future events. This is not an easy task since the data to compare with is not always available at the time of validation. Instead, the ability of the model to simulate the number of observed cases compared with historical data can be evaluated and compared with other models.

5.1.3 SENSITIVITY ANALYSES

This section focuses on parameter uncertainty. Besides validating that the model behaves correctly, sensitivity analyses should be performed to illustrate how the values of the input parameters influence the outcome from the model and thus the results of the economic evaluation. This is vital, since there often is uncertainty around the input parameters, which could potentially indicate uncertainty in the results from an economic evaluation and therefore also in its policy implications and the decision making that is based on the evaluation. It is also important to establish what parameters have the greatest impact on the results; if there is large uncertainty in those parameters, effort should be made to estimate those values as accurately as possible.

There are two major types of sensitivity analyses: deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The objective of DSA is to investigate parameter uncertainty and assess how the model outcomes are sensitive to changes in parameter values. The parameters are varied individually (one-way sensitivity analysis) or simultaneously (two or multi-way sensitivity analysis) and the effect on the outcome and the results from the health economic evaluation are observed. In PSA, all parameters are varied simultaneously, with parameter values being sampled from predefined probability distributions. The outputs can inform different forms of analysis, such as confidence intervals, and create the cost-effectiveness acceptability curve to investigate the probability that an intervention is cost-effective at different willingness to pay thresholds (9). PSA are more likely to be feasible in static cohort-based models than in population models that are based on a dynamic transmission model (11).

In a study by Ultsch et al (41), the authors found that the use of PSA is not common in dynamic models since it is computationally difficult to include parameter uncertainty that is affecting transmission. It is true, however, that PSA could provide a more comprehensive picture of the multidimensional uncertainty that is associated with the parameters of a model, but it lacks the transparency of DSA, where the effect of individual parameters variability on

the results are observed. A PSA can provide information about how likely a strategy or intervention is to be cost-effective, while DSA is used to determine for what parameter values a strategy is preferred. However, all parameters besides the one (or ones) being investigated are assumed to be true, i.e. have no uncertainty, in DSA, which is a limitation. In applying PSA, explicit probability distributions are required for the parameters. This could be problematic if, for example, the parameter values are based on data from a small patient population where the true shape of the parameter distribution is unknown (99). The uncertainty around the probability distribution is not captured in the PSA method.

In Studies I through IV, DSA has been applied to the results of the economic evaluations, both due to the structure of the models, and to ensure transparency, to illustrate how individual parameters influenced the results.

5.1.4 DISCOUNTING

Discounting is a mathematical procedure that adjusts future costs and health effects to present value to make costs and health effects that occur at different times comparable. The chosen discount rate can have a large effect on economic evaluations of vaccination programmes since there is often a delay in time between the initial expenditure and the health effects of averting a disease.

The theory of discounting health effects is based on the concept of positive time preferences (100), i.e. that individuals and societies prefer to benefit sooner rather than later. Thus, health effects that occur earlier are valued higher than those that occur later. The concept of positive time preferences can be used to understand individual decision making about behaviours that affect health, such as smoking or over-eating. It can also be used to understand societies' decision making about how to allocate health care resources to where it saves lives today rather than, potentially, more lives tomorrow, such as allocating funds towards cancer-treatment rather than preventive interventions that avert cancer occurring in the first place. There are several reasons to prefer benefits today rather than in the future, for instance having a short-term view of life, or feeling uncertain about the future and therefore preferring living today rather than thinking about tomorrow. Besides, there is also an opportunity cost related to consuming now rather than later, since the money that is spent today may instead have generated returns tomorrow (101).

The most common method of discounting in economic evaluation is to apply a constant discount rate to both costs and health effects, i.e. an exponential

discount rate. This is done by multiplying health effects and costs for each year with a discounting factor $(1+r)^{-t}$, where r is the chosen discount rate and t the time in years after the implementation of an intervention. However, there are alternatives to the standard discounting model, such as differential discounting (discounting health effects at a different rate than costs), non-constant discounting (a discount rate that changes over time), two-stage discounting (discounting intra-generational and inter-generational effects at a different rate¹), and delayed discounting (discounting health effects to another discount year than the time of intervention) (10). Most national guidelines recommend discounting both health effects and costs at a positive, constant, common rate back to a common point in time (10), and recommend a discount rate between 3% and 5% (see Table 5). Also, recommendations often include sensitivity analyses that vary the discount rate and applying differential discount rates, to explore how that affects the results (102). However, applying a differential discount rate leads to paradoxical interpretation of the results from a cost-effectiveness evaluation, since applying a lower discount rate for health effects than for costs makes infinite postponement of an intervention optimal in theory even though it is undesirable in practice (103).

Table 5 presents the recommended discount rates for costs and health effects for a set of European countries (104). The discount rates differ between the countries, where some apply a uniform discount rate, as Sweden and England, whilst some have a differential discount rate, as Belgium and the Netherlands. France distinguishes itself by having a time-dependent discount rate, with 4% during the first 30 years and 2% thereafter. The French discount rate implies that what occurs in the first 30 years after implementation is valued relatively lower than what happens in the longer run.

¹ A distinction should be made between the comparison of health effects of one individual at age a in time t and the same individual age $a+1$ in time $t+1$, and of one individual at age a at time t and another individual at age a at time $t+1$

Table 5 Recommended discount rates to use in health economic evaluations for costs and health effects in different countries (104)

| Country | Recommended discount rate | |
|-----------------|---|---|
| | Costs (%) | Health effects (%) |
| Sweden | 3 | 3 |
| Belgium | 3 | 1.5 |
| England | 3.5 | 3.5 |
| Estonia/Latvia | 5 | 5 |
| France | 4% if time horizon < 30 years and 2% thereafter | 4% if time horizon < 30 years and 2% thereafter |
| Hungary | 3.7 | 3.7 |
| The Netherlands | 4 | 1.5 |
| Norway | 4 | 4 |
| Poland | 5 | 3.5 |
| Scotland | 3.5 | 3.5 |

5.2 CONTINGENT VALUATION

Health and health improvements are not traded on a standard market, which requires the need for other ways to obtain estimates of the willingness to pay (WTP) of health improvements than to rely on the market.

Revealed or stated preferences are methods that are used to price a good for which a market price is missing. The *revealed preference method* systematically examines the preferences of decision makers or individuals as being revealed in the choices they make, in order to elicit the WTP for health improvements. That is, assuming that the preferences of consumers are being revealed by their observed habits (105) – we can infer a preference of good A over good B by observing an individual choosing A when B is available. Revealed preferences can be used to elicit WTP for choice sets that are already in place, but with an alternative approach, the *stated preference method*, we can derive WTP for new treatments and hypothetical interventions as well. Stated preference method measures individuals' preferences based on decision making in hypothetical choice situations. The stated preference method has been applied to a broader range than the revealed preference method, since it to a greater extent can be tailored to value specific conditions.

The most commonly used stated preference methods are the *discrete choice (DC) experiment* and the *contingent valuation (CV) method* (106). In a DC experiment, two or more hypothetical policies are presented to the participants of the experiment, and the participants are then asked to choose their preferred

option between the scenarios and the status quo. In a CV, the participants are presented with a hypothetical scenario that could reduce the risk of morbidity and/or mortality and are also presented with background information about the nature of the risk that the policy would reduce (107). The respondents are then asked to state their maximum WTP for the risk reduction that the policy entails, or told the cost of the policy and asked whether or not they are willing to pay that amount. CV is frequently used for the valuation of nonmarket goods (105, 108) and the contingent valuation method was used in Study V to elicit the relative willingness to pay for prevention in relation to treatment.

In a study by Johnston et al from 2017 (109), the authors present best-practice recommendations for stated preference studies. Among other things, it is recommended that the questionnaire clearly present the baseline condition, and how the policy influences that baseline condition. The information needs to be understood, accepted and regarded as credible by the respondent. A well-conducted CV survey should include a detailed description of the intervention being valued, questions about the WTP for the intervention, as well as questions about respondents' characteristics, such as age, income, education, etc. The WTP question should also define how the payment is made – for instance, if it is an out-of-pocket expenditure or financed via a general tax (109).

There has been criticism against the use of the contingent valuation method in valuing nonmarket goods. For instance, the problem of hypothetical bias arises when respondents state a WTP in a laboratory or survey setting that exceeds what their true WTP would be using their own money. One reason for hypothetical bias is “warm glow”, where the respondent states a higher WTP than their true WTP to get moral satisfaction (110). In addition, the particular format of a CV survey could influence the results – binary discrete choice questions in comparison to an open-ended question could result in different estimates.

Study V aimed to empirically investigate if there was a difference in the willingness to pay for preventive interventions and treatments for health improvements of equal magnitude in the general population. To perform the CV survey, a web-based survey instrument, the *Health Report* (111), was used to collect data on WTP for prevention and treatment, respectively. *Health Report* is a Swedish web panel with 3,995 respondents (in 2017). Data on the respondents' background were collected at the time of recruitment to the panel. The study began with an introduction (“cheap-talk”) and the respondents were then asked to answer four questions, divided into two parts. In the first part, a less severe skin disease was described and in the second part, a more severe

skin disease was described. The respondents were then asked to state their WTP for treatment and a preventive intervention that reduced the risk of getting the disease. The currency was Swedish krona (SEK), and the response was on a payment scale (112), constrained by a lower limit of 0 SEK, and an upper limit of 1,000,000 SEK. The WTP was defined as a one-time cost. The respondents had the option of commenting on the survey at the end.

5.2.1 STATISTICAL ANALYSES

In Study V, if and how the WTP differed for prevention and treatment was investigated, by controlling for severity of disease, and respondents' socioeconomic and demographic characteristics in regression analyses. To make the WTP for prevention and treatment comparable, the stated WTP was divided by its corresponding risk reduction to create a WTP that was adjusted for risk:

Equation 2

$$WTP_i = \frac{\text{stated } WTP_i}{\text{risk reduction}_j}$$

where i refers to the respondent and j to whether it is prevention or treatment.

The dependent variable WTP was continuous and constrained in range with a large mass point around zero. A two-part model was used, which is commonly used for analyses of skewed data (113). In the first step, the model estimates the probability of having a positive WTP, depending on the type of intervention, prevention or treatment, and the control variables. Specifically, and by applying a logistic regression, the calculation in the first step was as follows:

Equation 3

$$\Pr(WTP > 0) = \alpha + \beta_1 * Prevention_i + \beta_2 * Severity_i + \mu_i X_i + \gamma_i C_i + \varepsilon_i$$

Prevention equals one (1) for prevention and zero (0) for treatment. Severity equals (1) for the more severely ill health state, and zero (0) otherwise. X is a vector of exogenous characteristics of respondent i , and C is a vector of categorized comments by respondent i on the survey.

In the second part of the two-part model, the model estimates the magnitude of the WTP contingent on the WTP being positive. To reduce skewness, the WTP

was transformed to log-normal and then an ordinary least square (OLS) regression was run:

Equation 4

$$\ln(WTP|WTP > 0) = \alpha + \beta_1 * Prevention_i + \beta_2 * Severity_i + \mu_i X_i + \gamma_i C_i + \varepsilon_i$$

In both parts of the two-part model, robust standard errors clustered on individuals were used, to take the structure of the data into account (each respondent answering four questions). Subsequently, marginal effects were calculated for all observations, i.e. with the results from the first and second steps combined.

If the two error terms in the first and second steps of the two-part model were assumed to be uncorrelated, a simple OLS regression could have been run (114). However, it seems unlikely that the error terms are uncorrelated since there could be unobserved factors influencing both the probability of a nonzero WTP and the magnitude of the WTP. That makes the two-part model more suitable.

The Akaike's Information Criterion (AIC) and Schwarz's Bayesian Information Criterion (BIC) was used to test the relative goodness-of-fit of the model specifications and two-part model versus the OLS model (114).

5.3 ETHICAL APPROVAL

The Ethical Review Board in Stockholm (reference number 2017/1733-32) approved the study conducted in Study V. In Study I through IV, no individual data were used, and the studies were thereby not in need of an ethical approval.

6 RESULTS

6 RESULTS

In this section, the main results of each study are summarized. More details can be found in the referred studies, and a general discussion and conclusions are found in sections 7 and 8. A section that illustrates the impact of different discount rates on the results from health economic evaluation is included in the section that summarizes the results from Study I (see 6.1.1).

Study I through IV used a cost-effectiveness threshold of EUR 50,000. However, the level of EUR 50,000 is not an official threshold in Sweden, but rather assumed given earlier guidelines of what could be considered cost-effective (3), or based on previous decisions from the Dental and Pharmaceutical Agency in Sweden (4). In reality, there is no set threshold, and if there were, no guidelines link a threshold for treatment to a threshold for prevention and vaccination. Therefore, there are reasons to investigate the relative willingness to pay for prevention in relation to treatment, which was performed in study V.

6.1 STUDY I

Study I aimed at investigating the cost-effectiveness of expanding the Swedish HPV vaccination programme to also include preadolescent boys, by comparing health effects and costs of HPV-related disease for a sex-neutral vaccination programme versus only vaccinating girls. An age-structured population-based dynamic Markov model was developed that simulated the burden of HPV 16 and 18 in Sweden, accounting for herd immunity and sexual behaviour. The main outcome from the epidemiological model was the number of individuals with HPV-related cancers (cervical, genital, anal, and oropharyngeal cancer), and cervical intraepithelial neoplasia.

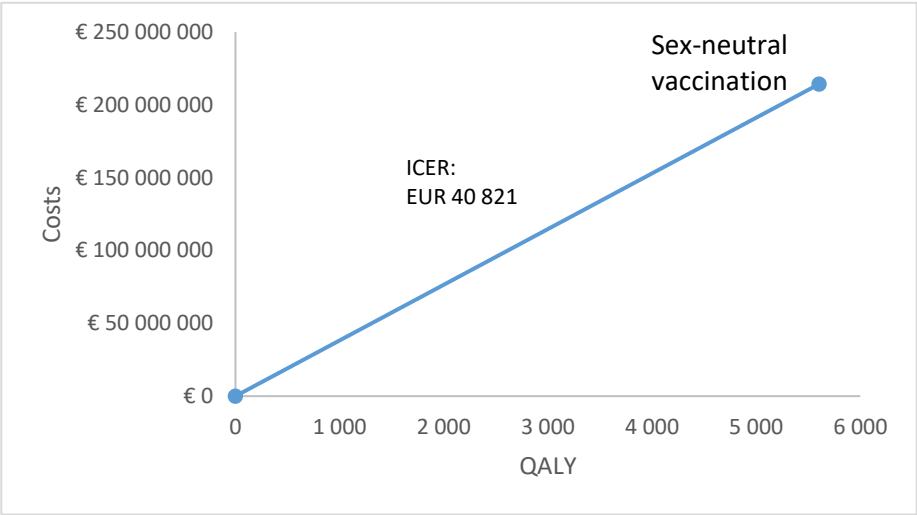
Over the modelled time horizon of 100 years, girls-only vaccination would lead to a decrease in HPV-related cancer among girls of 86% and boys of 69%. The corresponding figures for sex-neutral vaccination were 93% and 84% for girls and boys, respectively. Sex-neutral vaccination led to accumulated increased costs of about EUR 200 million and about 5,600 gained QALY over the time horizon, which resulted in an ICER of EUR 40,000 (see Table 6 and Figure 6).

The results were mainly affected by the number of HPV-related diseases included in the analysis, the discount rate (see section 6.1.1), and the price of the vaccine.

Table 6 Total costs, and total QALY gained for girls-only vaccination and sex-neutral vaccination and its related ICER

| | Girls-only vaccination | Sex-neutral vaccination |
|-------------|------------------------|-------------------------|
| Total costs | 142,071,488 € | 356,354,078 € |
| Total QALY | 62,399,875 | 62,405,479 |
| ICER | | 40,821 € |

Figure 6 Incremental costs, incremental QALY and ICER for sex-neutral vaccination in comparison to girls-only vaccination

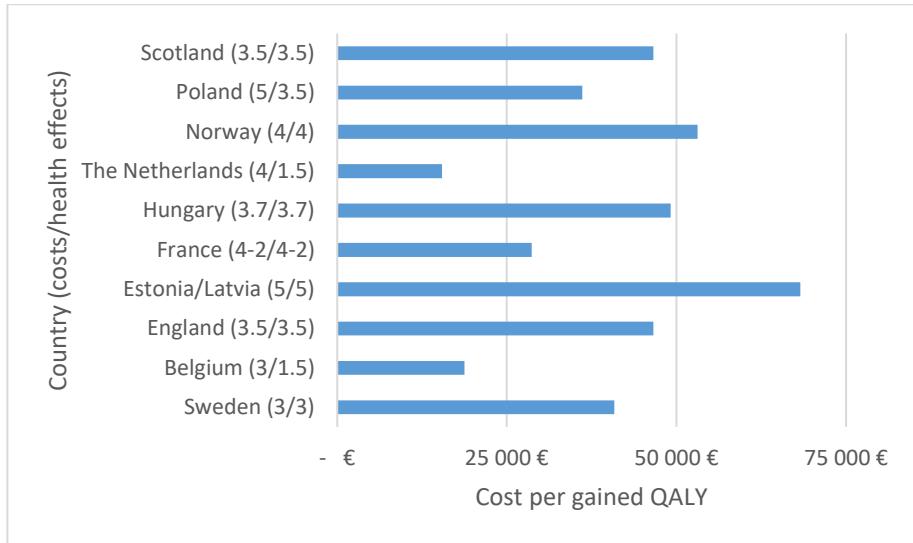


6.1.1 IMPACT OF DISCOUNTING

The impact of different discount rates on the ICER in Study I is presented in Figure 7. The results from Study I indicate an ICER of EUR 40,000 of including boys, in addition to girls, in a national HPV-vaccination programme, when applying the Swedish discount rate of 3%. By using different countries discount rates, the result ranges from EUR 15,500 (the Netherlands) to EUR 68,000 (Estonia/Latvia), which illustrates the importance and implications of the chosen discount rate. If a cost-effectiveness threshold of EUR 50,000 was assumed, this implied that HPV vaccination for boys, in addition to girls, would be considered cost-effective in, for instance, Sweden, but not in the neighbouring country Norway that has a discount rate of 4% for both health effects and costs. Even though the same assumptions are applied in the model, and the same epidemiological outcome from the models are received, the chosen discount rate would alter the interpretation of the results.

This analysis further highlights the importance of the chosen discount rate, and the importance of applying sensitivity analyses to display the impact of the discount rate on the results from a health economic evaluation.

Figure 7 Impact of applying different countries' discount rate (discount rate indicated in parenthesis cost/health effects) on the cost per gained QALY in Study I



6.2 STUDY II

The aim of Study II was to evaluate the cost-effectiveness of three alternative vaccination strategies for pertussis. A cohort-based deterministic decision tree model was constructed to simulate the incidence and severity of pertussis among otherwise healthy infants for four scenarios: 1, today's programme; 2, cocooning; 3, maternal vaccination; and 4, on-schedule vaccination, i.e. vaccine given at the exact right timing in the vaccination programme. The modelled time horizon was one year.

The results indicate that maternal vaccination would not be cost-effective (ICER: EUR 66,000) at a cost-effectiveness threshold of EUR 50,000, while on-schedule vaccination would be a dominant strategy, i.e. have a better effect at a lower cost, in comparison with today's vaccination programme (Table 7). Maternal vaccination would, compared to on-schedule vaccination, result in a cost per gained QALY of EUR 300,000 (the slope of the dotted line in Figure 8), which cannot be considered cost-effective. On-schedule vaccination and maternal vaccination were competing strategies, where maternal vaccination

was a complement to today's vaccination programme and on-schedule was an alteration of today's programme. However, the possibilities to implement on-schedule vaccination and to give the first dose of the pertussis vaccine exactly 90 days after birth per the programme cannot be deemed realistic, since such a strategy would be interrupted during summer holidays and weekends. Although ideally, the maternal vaccination strategy should be compared to the on-schedule strategy, since the two strategies were competing, the comparison between maternal vaccination and the current programme was reasonable.

As visible from Table 7, the cocooning strategy was dominated by the competing vaccination strategy of maternal vaccination, since it is both more costly and has a lower health effect in terms of gained QALY. Cocooning is therefore not a relevant vaccination strategy.

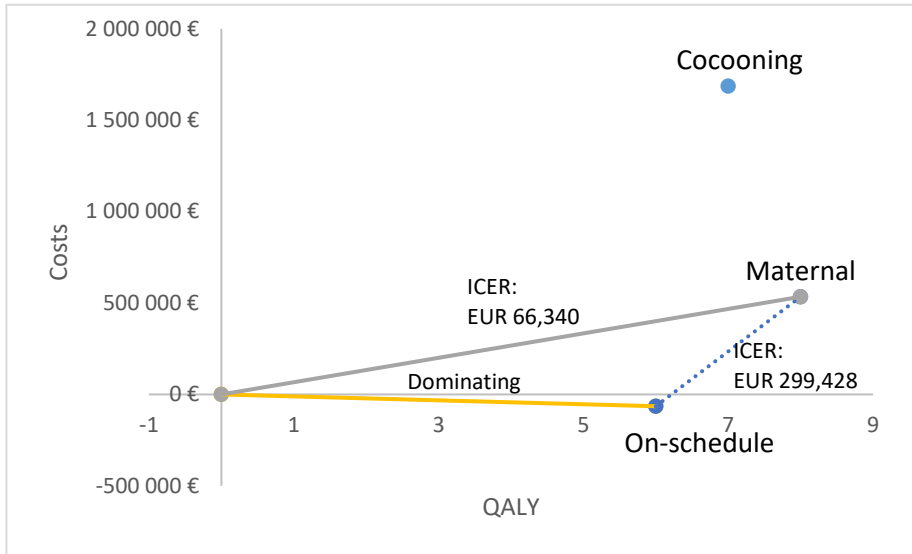
The results were all sensitive to assumptions of the annual incidence of pertussis among infants, and the analysis of the cocooning and maternal strategies were sensitive to the price of the vaccine for parents, as well as vaccination coverage among parents.

Table 7 Total costs, and total QALY gained for the different vaccination strategies against pertussis and its related ICER

| | Current programme | Cocooning | Maternal | On-schedule |
|------------------------------------|-------------------|-------------|-------------|-------------|
| Total costs | 708,732 € | 2,395,324 € | 1,242,988 € | 644,132 € |
| Total QALY | 109,079 | 109,086 | 109,087 | 109,085 |
| ICER compared to current programme | | NA* | 66,340 € | Dominant |
| ICER compared to cocooning | | | Dominant | |
| ICER compared to on-schedule | | | 299,428 € | |

*NA: not applicable since dominated by maternal vaccination

Figure 8 Incremental costs and *QALY* for the maternal and on-schedule vaccination strategy and related ICER, and the incremental cost and *QALY* for the cocooning strategy



6.3 STUDY III

The aim of Study III was to assess the cost-effectiveness of including pneumococcal vaccination for the elderly in the Swedish vaccination programmes. A cohort-based deterministic decision tree model, with a five-year time horizon, was developed to simulate the burden of pneumococcal disease with and without vaccination. The model accounted for invasive pneumococcal disease (IPD) and pneumococcal pneumonia and investigated the potential cost-effectiveness of vaccinating both a 65-year old cohort and a 75-year old cohort.

The results (Table 8) suggest that a vaccination programme would reduce the burden of pneumococcal-related disease significantly, both when vaccinating a 65-year old cohort and a 75-year old cohort. However, with an ICER of EUR 94,000, it could not be considered cost-effective to vaccinate 65-year olds, whereas vaccination of 75-year olds with an ICER of EUR 29,500 could be considered cost-effective. If the two vaccination strategies were considered as competitive, i.e. if the question were whether a 65-year-old cohort or a 75-year-old cohort should receive pneumococcal vaccination, vaccination of the 75-year-old cohort dominates the alternative strategy. Vaccination of the 75-year-old cohort gives rise to more gained incremental QALY (45 vs 27) at a

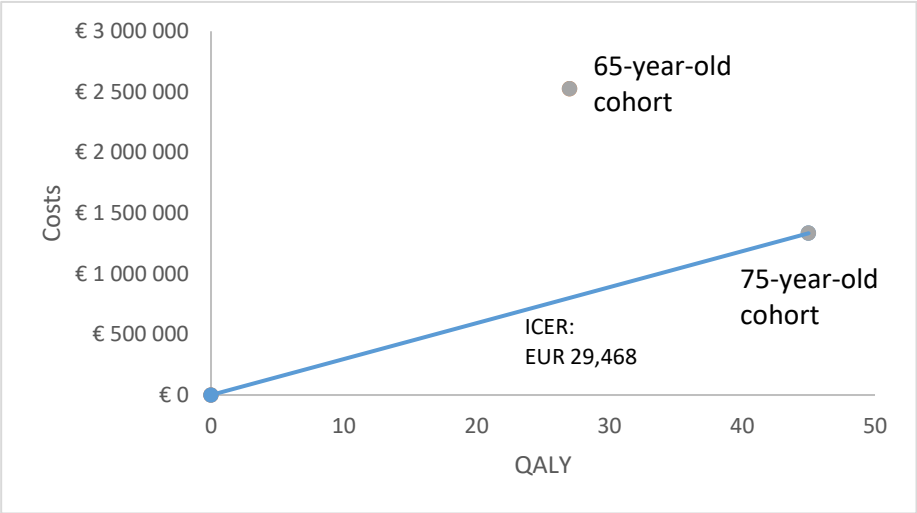
lower incremental cost (EUR 1,334,000 vs EUR 93,600) than vaccination of the 65-year-old cohort. This is illustrated in Figure 9.

The results were robust in sensitivity analyses, and varying the parameters did not alter the interpretation of the results. The most influential parameters were the vaccine effectiveness and the estimated share of pneumococcal disease that was vaccine-specific, as well as the proportion of individuals that needed an extra visit to get the vaccination.

Table 8 Total costs, and total QALY for pneumococcal vaccination for the two cohorts, and its related ICER compared to no vaccination

| | 65-year-old cohort | | 75-year-old cohort | |
|-------------|--------------------|-------------|--------------------|-------------|
| | No vaccination | Vaccination | No vaccination | Vaccination |
| Total costs | 4,227,857 € | 6,754,796 € | 6,334,237 € | 7,668,207 € |
| Total QALY | 412,973 | 413,000 | 281,874 | 281,919 |
| ICER | | 93,578 € | | 29,468 € |

Figure 9 Incremental costs and QALY for the 75-year-old cohort and the related ICER, and the incremental cost and QALAY for the 65-year-old cohort



6.4 STUDY IV

Study IV aimed at conducting cost-effectiveness analyses of introducing varicella and/or herpes zoster vaccination in the Swedish national vaccination programme. An age-structured population-based dynamic Markov transmission model of the varicella-zoster virus was linked to a health

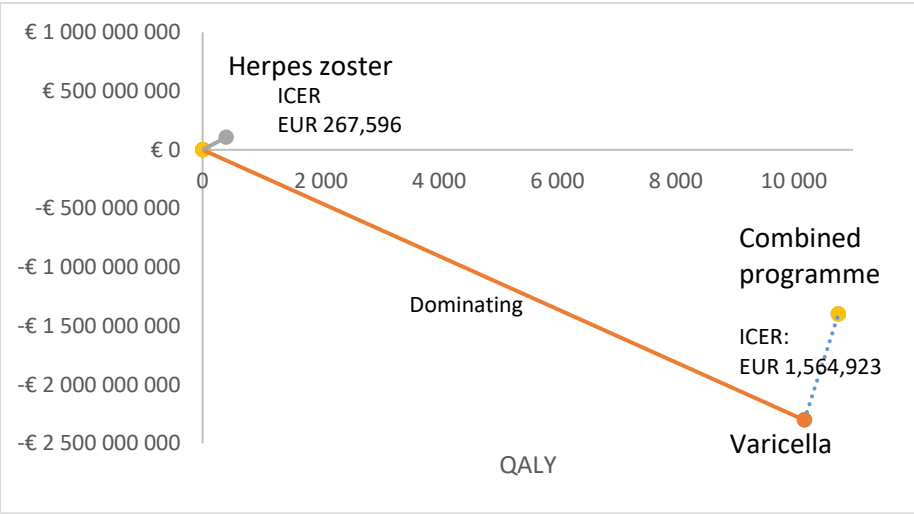
economic model. The epidemiological model accounted for various ways of contracting the diseases, such as natural infection and reactivation, break-through infection, and vaccine-derived infection, and accounted for indirect effects of vaccination through herd immunity.

The results (Table 9) indicated that vaccinating against varicella, with two doses at 12 and 18 months of age respectively, would be cost-effective and dominant compared to no vaccination. Vaccinating 65 year-olds against herpes zoster, however, cannot be considered cost-effective with an ICER of EUR 270,000 compared to no vaccination. The combination of the two programmes would also be cost-effective (dominating) compared to no vaccination, but this result stems almost entirely from the effect of the varicella vaccination. This becomes evident when investigating the ICER of the combined programme in comparison to the competing strategy of only varicella vaccination. The cost per gained QALY is then approximately EUR 1,565,000 (the dotted line in Figure 10), which is far from cost-effective in a Swedish setting. This suggests that the combined programme was no longer a relevant vaccination strategy.

Table 9 Total costs, and QALY losses for varicella and herpes zoster vaccination, and the related ICER compared to no vaccination as well as the ICER for the combined programme in comparison to varicella vaccination only

| 85-year time horizon | No vaccination | Varicella vaccination only | Both varicella and herpes zoster vaccination |
|---|-----------------|--------------------------------|--|
| Total costs | 4,954,209,906 € | 2,653,109,047 € | 3,555,059,372 € |
| Total QALY loss | 79,706 | 69,528 | 68,951 |
| ICER, compared to no vaccination | | Dominant | |
| ICER, combined programme compared with varicella vaccination only | | | 1,564,923 € |
| 20-year time horizon | No vaccination | Herpes zoster vaccination only | |
| Total costs | 2,270,562,594 € | 2,377,077,574 € | |
| Total QALY loss | 38,713 | 38,315 | |
| ICER, compared to no vaccination | | 267,596 € | |

Figure 10 Incremental costs and *QALY* for varicella vaccination and herpes zoster vaccination, the related ICER, and the incremental cost and *QALY* for the combined programme



6.5 STUDY V

Study V aimed to investigate if there was a difference in willingness to pay (WTP) between prevention and treatment for health improvements of equal magnitude. A web-based survey instrument was used to perform a contingent valuation study in a sample of the Swedish population assessing the WTP for prevention and treatment.

The results from the econometric analyses found that the respondents, on average, were less willing to pay for prevention than for treatment, but that those that were willing to pay for prevention had a higher WTP than for treatment. The latter effect was more substantial, and the results suggest that the WTP for prevention was 85% higher than for treatment. Also, the WTP increased with the severity of disease and income. Being born in Sweden, compared to any other country, also indicated a higher WTP. Commenting on the survey that health care should be financed through taxes was associated with a lower WTP.

Four potential mechanisms that may have driven the results were identified. Firstly, prevention (and vaccination) suggests that an individual does not have to be ill with a disease in the first place, implying a certain “insurance value” of vaccination. Secondly, the results may have been affected by the baseline risk, which is equal to one for treatment but much lower for prevention. However, how this influences the results are not straightforward.

Thirdly, a scale bias may be in place if the respondent is not sensitive to the change in risk reduction between prevention and treatment, and the different WTP reflects a change in attitude rather than the true WTP of the respondent and the respondent does not consider the absolute risk reduction. Since the absolute risk-reduction is lower for prevention than for treatment, this would imply a bias towards prevention. Before adjusting for the risk-reduction, the WTP was higher for treatment than for prevention. This suggests that the results were dependent on the respondents' ability to understand the concept of absolute risk reduction. The fourth mechanism that may have driven the results of a higher WTP for prevention, was that the scenarios in the survey describing prevention clearly stated that there was no cure for the health-state. This could further explain the higher WTP for prevention.

7 DISCUSSION

7 DISCUSSION

The overall aim of this thesis was to assess the potential cost-effectiveness of vaccination against infectious diseases and to investigate the relative willingness to pay for prevention in relation to treatment. This section discusses the findings and methodological matters of the thesis, as well as the limitations of the studies and ethical considerations.

7.1 METHODOLOGICAL REFLECTIONS

7.1.1 DECISION ANALYTIC MODELLING

In Study I through IV, decision analytic modelling (DAM) was used to perform economic evaluations of vaccination against infectious diseases. The economic evaluations aimed to answer the question of whether the cost of implementing the investigated vaccination or vaccination strategy in the national vaccination programme in Sweden would be reasonable in relation to its health effects.

DAM seeks to facilitate transparent decision making and satisfies five important objectives of economic evaluations, namely; *structure*, *evidence*, *evaluation*, *uncertainty and variability*, and *future research* (2). The ability of the DAMs included in this thesis to satisfy the above-mentioned objectives will be further discussed in this section.

- Structure of the model

The first objective of structure illustrates the importance of not using generic epidemiological models for economic evaluations of vaccinations. The structure must reflect all the relevant health states. In addition, the differences in the epidemiology of the investigated diseases, and the different transmission paths, indicate the importance of individually constructed models where the choice depends on the specific disease and the question.

Each of the four studies had epidemiological models built to specifically represent the transmission dynamics and the clinical manifestation of each infectious disease. Studies I and IV used a population-based dynamic Markov model structure to account for all effects of vaccination, while Studies II and III used a cohort-based static decision tree model structure. A cohort-based static model allows for direct comparison of the expenditures and benefits of the vaccinated cohort, with those of other investments, but may underestimate

the value of the vaccination programme in terms of health benefits to the whole population that is captured in a population-based dynamic model (11).

The diseases differed both regarding relevant health states and the effect of the vaccinations – vaccination can prevent a disease completely for the vaccinated, give rise to a milder form of the disease, or affect the transmission of the disease. The model should include the pathways of the disease, meaning the clinical representation for those infected, with and without vaccination (97). The transmission paths of the diseases differed greatly. High-risk HPV-types, which are the types that potentially could cause cancer, are sexually transmitted, in contrast to pertussis, which is transmitted via aerosolized respiratory droplets, and pneumococcal disease, which transmits via direct contact with respiratory secretions like saliva. Like pertussis, the varicella zoster virus can be transmitted via inhalation of aerosols or direct contact, but herpes zoster emerges via reactivation of latent varicella infection. This highlights the importance of disease-specific epidemiological models, that may differ in terms of design choices such as type of model (static or dynamic), what health states to include, and length of time horizon.

The chosen time horizon is important and needs to be set considering the natural history of the disease. If the impact of a vaccination programme is immediate, or the long-term evidence is scarce, a quite short time horizon may be the most relevant. On the contrary, applying a short time horizon for a vaccine that has effects long after its implementation will not capture all relevant effects, and may only give rise to resource use and its related costs, but not capture the resulting health effects. The time horizon should be long enough for a steady state to occur (41). For instance, the impact that varicella vaccination among children has on the burden of herpes zoster disease when the vaccinated children grow up would be disregarded if the time horizon is set too short. The time horizon in Study IV was therefore set to 85 years when evaluating varicella vaccination to achieve a steady state, but only to 20 years when evaluating herpes zoster vaccination.

To illustrate the impact of the chosen time horizon, the results from the economic evaluation can also, in addition to the full time horizon, be presented in steady state. Steady state is a situation where the full effect of a vaccination programme has been reached, i.e. when the epidemiological variation of a dynamic model ceases (11, 41), in contrast to the implementation phase. In the implementation phase, the costs of the vaccination programme are manifested but the savings from the programme as a result of the reduced burden of disease has not yet been established (41). Results from the implementation phase are useful for evaluating policy implications and decision making since they

reflect the true costs and health effects after the implementation of a vaccination programme, i.e. the full costs and health effects until a vaccination programme has reached a steady state. In research, however, the use of a steady state model is motivated due to its ability to show the effects once a programme has stabilized, i.e. when the full effects of vaccination are manifested.

- Evidence

There is some common evidence that is vital in every DAM of vaccinations, such as the burden of disease without vaccination, and the effect of a vaccination programme on that burden.

An economic evaluation of vaccinations is only as good as the epidemiological evidence that provides the basis of the evaluation. The strength of the evidence behind the input data in the DAM should be clearly stated and described (41). All of the studies included in this thesis state what epidemiological and economic data have been applied in the models. The data have been obtained and applied in collaboration with clinical experts on the specific disease. However, data were not always available, for instance regarding the HPV prevalence in the Swedish population. In such situations, assumptions have had to be made together with clinical experts. In the case of HPV prevalence, we assumed that the effect on HPV-related cancers, which was the main outcome from the evaluation, was equivalent to that of the effect on HPV. Even if this was an assumption, in the absence of other reliable data, it constituted the best input at that time.

- Evaluation

The third objective, evaluation, concerns the ability to transform the evidence from the epidemiological model into health effects and costs to investigate if the costs of the intervention are reasonable in relation to its health effects. The costs that are included in an economic evaluation depend on the perspective of the analysis, and the perspective depends on the relevant decision context and should be specified since it can alter the interpretation of the results (11). Data on the resource use and its related costs have been obtained and interpreted in collaboration with clinical experts on each specific disease in Studies I through IV.

One often debated issue in health economic evaluation is the inclusion of production losses. In the narrow interpretation of production losses, only those that are part of the workforce can give rise to production losses, i.e. not children or retired individuals. This indicates that vaccinations that target children or

the elderly may have a less beneficial cost per gained QALY, than vaccinations targeting those in the workforce.

Even though the QALY measure is established as the leading health effect measurement in cost-effectiveness analyses, there are limitations to its application, and several issues have been raised, both ethical and methodological, as well as context-specific (22). One of the most common objections concerns the valuing of one life over another life, and that a perfect state of health does not make a life more or less valuable. For instance, it cannot be assumed that an individual in a wheelchair is automatically not living life as happily as an individual that is not in a wheelchair (115). The linearity of the QALY has also been subject to criticism, i.e. that a QALY is valued the same no matter the baseline health, or whether the evaluation relates to end-of-life treatment or not. The notion of “a QALY is a QALY is a QALY”, which often is cited in the world of health economics, indicating that all QALY are considered equal, and all increases are valued the same regardless of where the increase occurs. An increase of 0.2 to 0.4 is valued the same as an increase from 0.6 to 0.8, even though one can argue that an improvement on the lower spectrum of the QALY could impose a greater impact on an individual’s health and quality of life, than an increase on the upper spectrum.

Criticism also targets the validity and reliability of measuring the utility of health (22), since different populations tend to value health differently, e.g. the general population, the patient population, and a physician may very well have different preferences and thus differ in their valuation of a health state (116). The same argument applies to populations from different countries with different cultures and for different periods in time. The QALY measurement has also been critiqued for not being sensitive enough to small but clinically meaningful changes in health, which could be very important in certain sub-populations.

- Uncertainty and variability

Uncertainty and variability, the fourth objective, is related to the ability to investigate how sensitive the results are to variation in the included parameters. One way to deal with uncertainty is via extensive sensitivity analyses. It also relates to structural uncertainty around the model, which is investigated via calibration and validation of the model.

In Studies I through IV, deterministic sensitivity analyses (DSA) were used to explore the uncertainty of the results of the economic evaluations. This was both due to the structure of the models since it could become computationally

intensive (as in Study IV) to apply probabilistic sensitivity analyses (PSA), and for transparency, since we sought to illustrate how individual parameters influenced the results. As the economic evaluations were performed also to inform decision makers, using DSA may enhance the understanding of policy implications because it can be more easily understood, e.g. what would happen if the age group targeted for elderly vaccination was changed to 75 and older instead of the current 65 and older?

Vaccination has several distinctive features (117), one of them being that the final health outcome sometimes manifests a long time after the intervention. For instance, even if boys are vaccinated against HPV at the age of 11-12, the real effect in terms of HPV-related cancer cases avoided will not be observable until some 50 years later. There may also be a delay between the intervention and the realization of herd immunity. The long time between the time of intervention and the time of effects could give rise to uncertainties in the analyses – what will health care look like 50 years in the future? One way of dealing with that uncertainty is discounting. As illustrated in Figure 7, the choice of discount rate could potentially affect the conclusion of a DAM.

- Future research

The fifth and final objective, future research, identifies the prioritization of future research through the assessment of uncertainty. After conducting an economic valuation using DAM, the areas in need of future research often surface. For instance in Study IV where the duration of vaccine protection after two doses of varicella vaccine was uncertain in the long-term (118) and where long-term impact and immunity needs to be followed, or in Study III, where more data is needed for serotype-specific and age-specific vaccine effectiveness.

7.1.2 CONTINGENT VALUATION

Study V aimed to investigate if the willingness to pay (WTP) for prevention would differ from the WTP for treatment for health improvements of equal magnitude, and if so; how? In contrast to treatment, which treats an already manifested disease or health state, vaccination, as a preventive measure, entails vaccinating individuals against possible future ill health. The main finding in the study was that WTP for prevention on average was higher than WTP for treatment. This implies that individuals valued health gained through prevention higher than health gained through treatment. The results suggested that individuals were less likely to have a WTP for prevention than for

treatment, but among those that had a WTP greater than zero, the WTP was higher for prevention than for treatment.

We used contingent valuation in Study V, and some restrictions to the method are important to be aware of. For instance, we used a constrained payment scale, which is subject to limitations. Respondents could revise their true WTP estimates, either up- or downward, to fit the constraints (119). This could, in turn, lead to skewness in the data and many zero-responses (120). The many zero-responses could be mitigated by using a closed set of responses instead of a text-box that was used in Study V.

There is a risk of strategic responses in CV-studies, i.e. that respondents state a higher WTP than their true WTP would have been if they were to use their own money. To ease this effect, an introductory letter was used in Study V that specifically stated the purpose of the study. It could be hard for respondents to imagine a described disease without all the relevant components of scenarios such as severity, and duration, which highlights the importance of a concise and informative description of the disease.

The rationality of economic agents is a well-researched area in economics (121), and the exclusion of irrational respondents could result in valid preferences being eliminated. Therefore, a sensitivity analysis was performed investigating how this exclusion affected the results.

7.2 LIMITATIONS

In all studies, we used the best available epidemiological data. When no data were available, we have used clinical expertise to estimate the value of parameters. For instance, in Study I, the evaluation relied on the proportions of the different HPV-related cancer types that were attributable to HPV-infection rather than adapting a transmission model, since we did not have reliable data on the prevalence of HPV infection in Sweden among different age groups. This was a limitation of the study. In Study III, we had very limited data on the effect of vaccination in the age group 75-years and older, but concluded, in collaboration with clinical expertise, that the data we used was the best available at that time.

Study II and Study III had relatively short time horizons. In Study II, the main reason for that was that steady state was achieved already during the first year after implementation of the vaccination strategies since infants were investigated. For Study III, the reason was the uncertainty of the duration of the protective effect of a vaccination programme since serotype replacement

could continue to evolve in the future. If we had been able to capture that uncertainty via better data, a longer time horizon would have been preferred. In Study IV, results were presented in steady state in a sensitivity analysis to illustrate the effect of the chosen time frame (herpes zoster). A similar analysis could have been performed in Study I, and would then have shown a more favourable cost per gained QALY once the programme has stabilized.

In Study II, three alternative vaccination strategies were evaluated in comparison with the current vaccination programme against pertussis. Since the strategies were competing, they should instead have been evaluated in comparison with each other than compared to no vaccination.

A unique characteristic of vaccination is that it does not only reduce the burden of disease for those vaccinated, but also indirectly protects other susceptible against infection, and can give rise to herd immunity (117). Study I and Study IV take herd immunity into account – the infectiousness in the models are affected by the share of vaccinated in the population, whilst Study II and Study III disregard the potential impact of herd immunity. The reason for disregarding the effect is two-fold; the time horizon is too short for the vaccinated individuals to affect the overall transmission of the disease, and the targeted population is too small to have an impact on overall transmission. However, the exclusion of a potential herd immunity effect will underestimate the effect of the vaccination (97). If the effect of herd immunity had been included, this would lead to more precise estimates of cost-effectiveness in the studies.

The inclusion of production losses serves a purpose for policy implications – a reduced burden of disease will, in many cases, ultimately have an impact on the production of a society. However, the need for the inclusion of production losses in research is not as evident. In Study I and Study III, production losses were not included in base-case analyses, but they were included in Study II and IV. In Study II, the results were only presented with the inclusion of production losses, which is a limitation of the study that decreases the comparability of the results. Study I and IV presents the results both with and without production losses, but differ with regards to the base-case analyses. In the consensus framework by Ultsch et al (41), they conclude that a societal perspective should ideally be considered as the base-case analysis, which is true in Study IV.

The cost of intervention in Studies I-IV was estimated using the list price of the vaccines, and the cost of administering the vaccination. It is highly likely that a vaccine against a disease that is part of a national vaccination programme would reach a much lower price level than the list price through procurement.

However, procurement prices are often not official and could change in each procurement process, why we choose to use list prices. The use of list prices in the evaluations thus may not reach the true results, which is a limitation of the studies. To mitigate this limitation, a graph has been included in Study I, Study III, and Study IV that illustrates, when applicable, how the cost per gained QALY changes when the price of the vaccine decreases all the way down to zero.

In Studies I through IV, we used QALY to measure health effects. The QALY-weights were obtained from published literature. However, we did not perform sensitivity analyses on the applied QALY-weights in any of the studies, which is a limitation since the results might have been sensitive to changes in the estimates.

To illustrate how the chosen discount rate affects the results, sensitivity analyses were performed in Study I and in Study IV where the discount rate was varied. A limitation of Study III was that the discount rate was not varied in sensitivity analyses, but since the time horizon was relatively short, it may not have influenced the results to any greater degree.

A further limitation of Studies I through IV, is that a PSA has not been applied as a complement to the DSA performed. Using a PSA could further have illustrated the multidimensional uncertainty and the probability of an intervention to be cost-effective.

We used a constrained payment scale in Study V, which was subject to limitations since respondents may have revised their willingness to pay to fit the constraints. This could have caused the skewness in our results with many zero-responses, which was the case in our data. However, it was not skewed to the left, which suggests that the high upper constraint did not bias the results upwards.

Another limitation of Study V is the underlying assumption of the willingness to pay to be proportional to the risk-reduction and not diminishing. The stated WTP was adjusted for the risk-reduction and this adjustment drives the results to a great degree. Also, the questions in the survey were not randomly ordered, indicating that ordering effects were not controlled for, which is another limitation of the study. In addition, the underlying health of the respondents in the study was not controlled for.

7.3 OVERALL DISCUSSION AND ETHICAL CONSIDERATIONS

The use of cost-effectiveness analyses as the evaluation technique of vaccinations and vaccination programmes comes with shortcomings.

As mentioned throughout the thesis, there is no official cost-effectiveness threshold in Sweden. Having an official threshold could strengthen the transparency in decision making and make decision making within the health care sector more straightforward, given that the threshold would be set to identify interventions that are good or very good value for money. However, it is also important to note that at a technical level, cost per gained QALY estimates are a product of economic modelling and generally based on several assumptions about population, efficacy, etc. Having an official threshold that is set too low would lead to investments in the health care sector that are too low relative its value, whilst setting the threshold too high would result in inefficiently high spending and losses on the market (122).

In the case of vaccination, the research question may be relating to a new disease to be implemented in a national vaccination programme targeting a specific population, or relating to an alternative vaccination strategy to be evaluated. Identifying competing interventions and including them in the analyses enhances the transparency and interpretation of the results. The need for identifying and comparing competing interventions also relates to the ethical considerations of an economic evaluation.

Economic evaluations aim to use resources targeted to the health care sector in the most efficient way, but interventions that are not cost-effective can be disguised as cost-effective in combination with other interventions. If that would occur, the allocation of resources will no longer be efficient. In Study IV, the combined vaccination programme with both varicella and herpes zoster appears to be cost-effective and even cost-saving when the comparator was no vaccination. However, when comparing the combination programme to the competing strategy of only varicella vaccination it becomes obvious that the added intervention of herpes zoster vaccination did not drive the results, and that the combination programme was not cost-effective. A failure to report the incremental analysis would thus imply that decision makers do not have all the information needed, and the allocation of resources would not be efficient. This further emphasizes the need for identifying all interventions, as well as the feasibility of the vaccination strategies, when evaluating the introduction of a new disease in a national vaccination programme.

It is stated in the Communicable Disease Act that vaccination against a disease must be cost-effective to be included in the national vaccination programme in Sweden (123). However, this alone should not be the decision basis to include a disease in the Swedish vaccination programmes. The vaccine must also affect the burden of disease and be ethical from a humanitarian standpoint. Also, the principles of human dignity, need and solidarity, as well as cost-effectiveness stated in the ethical platform, should guide all prioritizations made in Swedish health care (7).

The need for ethics in health economics is not clear, since it stands for itself but is included together with ethical considerations, when decisions and prioritizations are made. Health economics and health economic evaluations of interventions could be criticized for putting a value on health, something that cannot be valued according to some. However, as there is a demand that exceeds the supply on the health care market, prioritization must be done (2). From an ethical, as well as an efficiency, perspective, the prioritization should be carried out transparently and systematically, considering the cost and consequences in terms of health effects of alternative actions. Economic evaluations can be used to make more rational choices and to use resources in an efficient manner, but the ethical guidance is not covered by an economic evaluation.

Even though the results from Study V suggests that vaccination as a preventive measure should not be valued less than treatment for a manifested disease, preventive interventions are not always prioritized. One reason for that could be the “rule of rescue”, i.e. the need individual feel to save endangered lives when possible. That entails that more resources are allocated towards the treatment of manifested disease, whereas the same resources could have been used for prevention such as vaccinations that could imply that the disease would not occur in the first place.

Vaccination interventions indicates that a rather large population needs to go through a procedure that may prevent them from a disease sometime in the future. Although vaccines have a good safety profile, are held to a high safety standard, and severe adverse events from vaccination are unusual (124), vaccinations are still a health care intervention. Occasionally, vaccinations are used to protect others in society, as for maternal vaccination for pertussis that aims at protecting newborn infants. This instrumentalization of individuals, i.e. using them to protect others, is an ethical issue with no apparent solution. However, vaccination programmes contribute to an equal society, since all vaccines in the national vaccination programmes in Sweden are provided free of charge.

As stated throughout this thesis, resources are limited in the health care sector at the same time as the demand for health and health care are unlimited. This is the basis for the need for prioritization. Health economic evaluation and cost-effectiveness analyses provide a framework for conducting this prioritization in a transparent manner and with the explicit purpose to maximize health given the resources at hand. Vaccination, a preventive intervention that reduces ill health before it occurs, should also be a part of this prioritization, which is why cost-effectiveness analyses should be as frequently applied on new vaccinations and vaccination strategies as they are on pharmaceuticals and medical technology.

One of the unique characteristics of vaccinations is that they can give rise to great health effects many years from now, but there may be no health effects in the immediate future. Why would a decision maker invest a significant sum of money in an intervention that would not pay off in a long time, maybe not even in his or her lifetime? That is one of the hardest messages to get through to decision makers – to make them realize that the value of vaccinations may be lower than for treatment in the short run, but that vaccinations are one of the most efficient ways to reduce the burden of disease and save lives in the long run – that the value of prevention potentially is great, to society and individuals both.

8 CONCLUSION

8 CONCLUSION

This thesis adds to the research on cost-effectiveness analyses of vaccinations and the discussion of the value of preventive intervention in relation to treatment.

The results from the economic evaluations included have had or will have an impact on the vaccination programmes in Sweden, and the methods and knowledge will contribute to future policy-making and prioritization in the health care sector. Since all infectious diseases behave differently, both when it comes to the transmission of disease, the time horizon over which they occur, and the effectiveness of available vaccines, there is a need for specifically developed models for each health economic evaluation of vaccination. Additionally, the findings from the contingent valuation analysis contribute to the on-going discussion on the appropriate cost-effectiveness threshold and emphasize the need to prioritize prevention in health care.

9 FUTURE PERSPECTIVES

9 FUTURE PERSPECTIVES

As new data emerge on the long-term effects of vaccinations, there will be reasons to update their economic evaluations, as well as if there are changes in the understanding of the epidemiology or in the epidemiology itself. New models can ideally incorporate herd immunity to allow for analysis of the indirect effects of the vaccine against pertussis and pneumococcal disease, which could potentially lead to a more accurate cost per gained QALY. New data on the safety of maternal pertussis vaccination for infants born to vaccinated women from England and North America suggest that the Swedish evaluation could be updated by adding new components to the cost-effectiveness analyses.

New vaccines and new vaccine-types are constantly being developed, which will prompt new economic evaluations to be performed. The COVID-19 pandemic has led to completely new vaccines being tested on humans, such as RNA-vaccines, just a few months after the discovery of the virus. The methodology of economic evaluation needs to be further developed to capture relevant effects of transmission, such as traveling, or the effect of other interventions than vaccinations, such as social distancing. The broader value of vaccinations could also be further investigated, as for instance, its impact on antimicrobial resistance.

In Study V, we investigated how the WTP differed between prevention and treatment for a pre-defined skin disease of varying severity; it is probable that the ratio between prevention and treatment that was observed is more likely to conform to the ratio for diseases with similar severity. To be able to generalize the results and reach a more extensive conclusion on the ratio between prevention and treatment, future research should focus on applying a similar study design to a range of infectious diseases.

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